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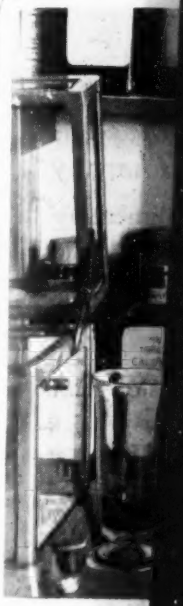

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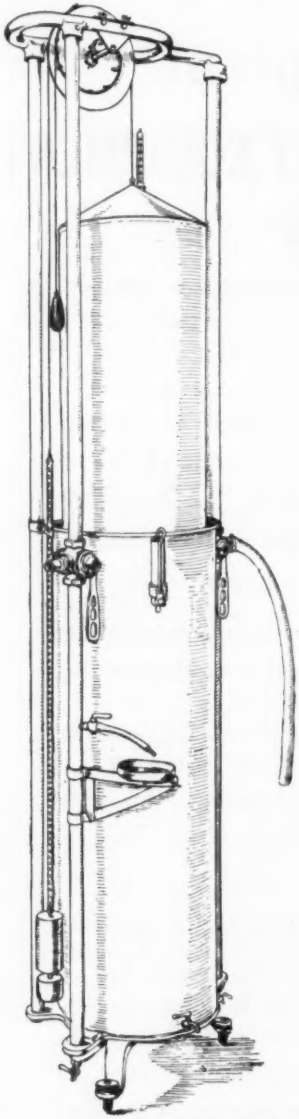

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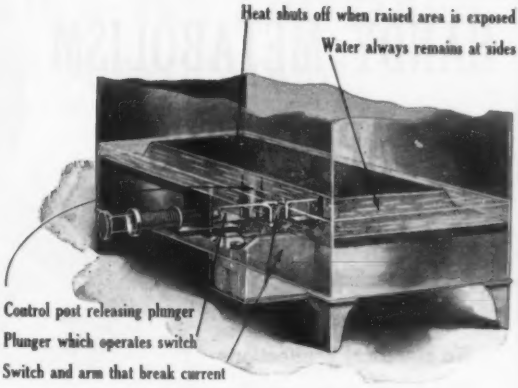
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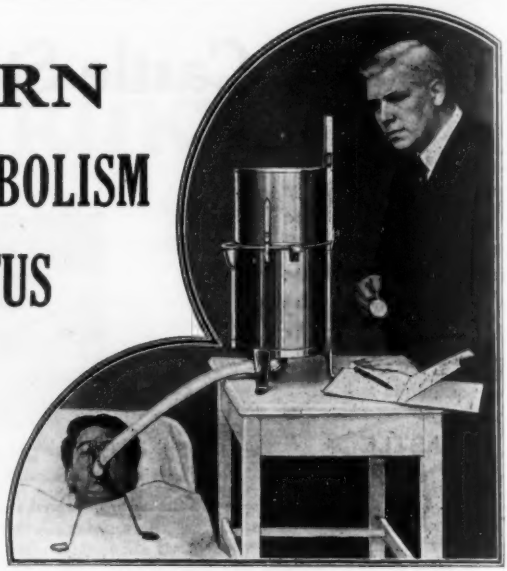

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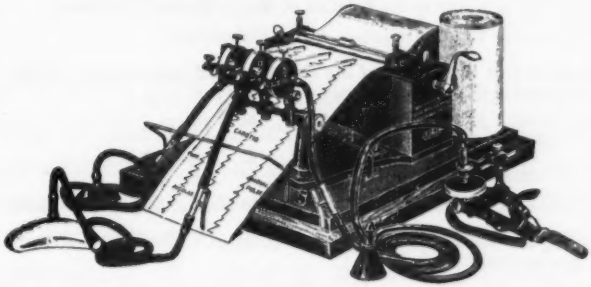

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ORIGINAL ARTICLES.

ENDOCRINOLOGY AS A KEY TO THE SOLUTION OF MAJOR MEDICAL PROBLEMS.*

By Charles E. de M. Sajous, M.D.,

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The opening scientific address of a new society should logically embody a review of the actual status of the field to which its labors are to be dedicated. In the present instance this custom assumes almost the importance of a duty, in view of the fact that at no time in its history has endocrinology, with the exception of the diseases of the ductless glands themselves, stood in a more precarious condition than it does today, particularly in this country. The physiologists, as will be shown presently, having failed to discover the functions of these organs notwithstanding painstaking efforts to do so, have left the endocrinologic ship, as it were, without a rudder, in so far as the clinician is concerned, as a guide for sound investigation, particularly in pathogenesis and therapeutics. The inevitable result, which I tried to forestall many years ago, has been to divide the profession at large into two camps: The ultraconservatives who are, with just cause, frightened off by the maze of groundless and unsupported theories with which the whole subject has been surrounded in recent years, and the overconfident who are the authors of the unwarranted theories and who administer organic products in practically all disorders without regard for physiologic effects. Even this overenthusiasm is to

* Read by invitation at the first scientific session of the Endocrinological Society of the city of New York, January 6, 1922, and before the Mercer County Component Society, Trenton, N. J., February 8, 1922.

be attributed, however, to the absence of knowledge concerning the role of the organs themselves in the body. Indeed, five years ago Prof. W. S. Halsted, of Johns Hopkins, after a serious effort to elucidate an endocrine problem, was finally led to conclude that "it must be evident to everyone that there reigns the greatest confusion on the subject of the functions of the glands of internal secretion." Today he might say with equal justice that this applies as well to the whole domain of endocrinology as it is generally interpreted, and that the confusion is steadily growing apace with time.

Might there not exist an intermediate class of clinicians who practice what might be termed scientific endocrinology? That there exists such a group it is my privilege to assert. After reviewing in greater detail the underlying cause of the prevailing confusion, the absence of adequate physiologic information, I will submit the reasons which led to the elaboration of this higher aspect of endocrinology and, by a few examples, briefly portray what it would mean to medical progress if its teachings were generally adopted in lieu of the present chaos to which the term "endocrinology" is attributed.

The Physiology of the Endocrines as Interpreted by Physiologists Affords no Aid to the Clinician. In making this statement, assurance may be given that there can be no question on my part of antagonism to physiology. Indeed, for the last forty years, first as professor of physiology in the Wagner Institute of Science in the early eighties, as editor of the *Annual of the Universal Medical Sciences*, in which Prof. Newell Martin and Howell, of Johns Hopkins, were my valued collaborators, and recently in the presidential address before the Association for the Study of the Internal Secretions,[1] I earnestly urged the importance of coöperative harmony between physiology and clinical medicine as a *sine qua non* of medical progress. It is the lack of this feature which, as we shall see, has prevented to this day the discovery by physiologists of the functions of any ductless gland, without a knowledge of which the clinician—meaning thereby the physician, the pathologist, the surgeon, the specialist, etc.,—cannot work out his own problems. His normal source of information, in view of his own arduous occupations, is the text-book of physiology. What does he find even in the best of these works?

Beginning with the adrenals the truth soon asserts itself. Despite the pioneer labors of Brown-Séquard in 1856; despite the convincing researches of Oliver and Schäfer upon their cardiovascular tone theory, of Abelous and Langlois upon their antitoxic theory, of Cannon upon his emergency theory and others—all have virtually been swept by the wayside. If the clinician tries to solve for himself the problem in question with the aid of physiologic literature he soon finds himself in a maze of contradictions con-

tributed by undoubtedly able men, but which, nevertheless, leave as leading impression a suggestive unreliability of their work. And yet a few physiologists, Stewart[2] and Gley[3] and their followers, overlooking the fact that experiments in *normal* animals can only, from the standpoint of exact science, portray the effects of precisely similar experiments in *normal* men—since any degree of pathology, a toxemia, the defensive process, organic lesions, etc., modifies the whole picture—have recently published interpretations of some clinical aspects of endocrinology, notably adrenal insufficiency, which close scrutiny and clinical experience fail totally to sustain. Nor can it be otherwise in the absence of any foundation for their argument. Indeed, physiologic knowledge on this score was frankly expressed by Swale Vincent,[4] now professor of physiology in London University, when he wrote, "We know nothing of the adrenal body on its own account."

The situation concerning the thyroid is quite as unsatisfactory. Notwithstanding the labors of Schiff, begun in 1856, which soon followed those of Reverdin and Kocher in the clinical field, and the later investigations of Horsley, Jeandelize and others, all affording ample proof of the influence of this organ upon nutrition and metabolism, Prof. Howell,[5] of Johns Hopkins, states in the last edition of his text-book of physiology that "no explanation has been furnished in respect to nutrition"; and that "the details of its influence on metabolic processes are for the most part unknown." Hence the fact that confusion also reigns in the clinical field. Since Kendall isolated the active principle thyroxin,[6] which profoundly accelerates metabolism, his (admittedly theoretical) view is that its function is "to furnish the animal organism with ammonia resulting from the deaminization of amino-acids." But it is at best difficult to reconcile this process with the increased intake of oxygen, following the feeding of thyroid, which varies from 20 to 75 per cent in myxedema and 10 to 40 per cent in animals, and the corresponding output of carbon dioxide. Nor does it explain the increased elimination of phosphoric acid observed by Chittenden and others or the familiar rapid reduction of fat which thyroid preparations provoke. While Kendall's conception may be sound, the manner in which the thyroid hormone influences nutrition and metabolism remains as obscure as it has ever been.

The physiologic functions of the parathyroids are no more lucid. The etiologic connection between removal of these organs and fatal tetany, first pointed out by Gley, has been shown to apply to carnivorous and about one-half of herbivorous animals. But how the parathyroids carry on the surmised process of breaking down the spasmogenic wastes is admittedly unknown. As Prof. Brubaker,[7] of Jefferson College, states, "It is evident that the subject needs further investigation."

The thymus also belongs to the "obscure" series, the more recent

experimental labors having virtually eliminated all importance to the functions formerly attributed to them. Howell[8] states in this connection that "the physiology of the thymus is very obscure; in fact, nothing that is definite can be said about its functions, except perhaps that the gland is concerned in some way with the processes of growth."

The pineal is no better off. After summarizing the investigations upon this organ, Prof. Schäfer,[9] of Edinburgh University, concludes with the statement, "It must be admitted that the results of clinical observations and experimental work in animals are at present difficult to reconcile and do not enable us to come to any definite conclusion regarding the functions of this organ and the nature and mode of action of its autocoids."

Concerning the pancreas, its internal secretion is now recognized as separate from that poured into the intestines. About all that may be considered established, however, even though pathologists have contributed much to the subject, is that the islets of Langerhans carry on some specific function—probably in sugar metabolism. Howell states that "the nature of this function and its relation to that of the acinar glands must be considered at present as open questions."

The functions of the pituitary body are equally obscure. Acromegaly is attributed to excessive secretory activity of the anterior lobe, but ample experience has shown that extracts of this lobe, even in enormous doses, or Robertson's tethelin, fail to cause growth in human beings or anything suggesting acromegaly. Again, the posterior pituitary, the source of the very efficient hypophysis sicca, pituitrin, etc., is supposed to represent a secretion. But, as Prof. Swale Vincent,[10] of London (and also Biedl), in keeping with my own previously published views, says of this lobe, "It is extremely difficult to imagine how such a structure can be regarded as a secreting gland." The same physiologist also states, "We know, after all, very little about the normal functions of the pituitary—no more, in fact, than we know about those of *any other of the ductless glands*." *

Such disappointing results would seem to be offset by the discovery of the endocrine active principles, some of which, at least, are serving so useful a purpose in every branch of practice. But, in truth, credit for them does not belong to physiologists. Abel, who gave us epinephrin, is a pharmacologist. Takamine and Aldrich, who discovered adrenalin, are chemists associated with manufacturing pharmacists. Kendall, who isolated thyroxin, and Robertson, who isolated tethelin, are both chemists.

The endocrines reviewed suffice to illustrate the inability of physiology alone, even as interpreted by its masters, to aid the

* All italics are my own.

clinician interested in the endocrinologic field. Any unbiased observer would conclude, in fact, that labors which had given such a paucity of results after researches covering the whole period elapsed since Claude Bernard introduced the term *sécrétion interne*, over sixty years ago, should be relegated to the long list of abortive efforts.

And yet would any degree of exclusion of physiologic labors be justified by facts? No greater calamity could befall endocrinology than such a course. During the period mentioned physiologists have accumulated a vast store of sound physiologic data which are invaluable in the development of this new branch of science, but their true worth is only brought to light, we shall see, through harmonious coöperation with other branches of medical knowledge, including, particularly, clinical medicine and pathology.

The Coöperation of Various Medical Sciences Necessary to Ascertain Endocrine Functions. Although it was Brown-Séquard, a physiologist, who gave the first impulse in 1856 which started modern endocrinology on its active career, the internist, realizing fully that to each quadruped, dog, cat, guinea-pig, frog, etc., studied by physiologists, he, as practitioner, pathologist, histologist, etc., studied hundreds of bipeds, men, women and children, soon learned from experience what a great physiologist, Pawlow,[11] emphasized twenty years ago, referring to the discovery, by clinicians, of the gastric secretory nerves, when he wrote: "Physiologists, on the other hand, had *fruitlessly endeavored for decades** to arrive at definite results upon this question. This is a striking but by no means isolated instance where the physician gives a more certain verdict concerning physiologic processes than the physiologist himself; nor is it indeed strange. The world of pathologic phenomena is nothing but an endless series of the most different and unusual combinations of physiologic occurrences which *never make their appearance* in the *normal* course of life. It is a series of physiologic experiments which Nature and life institute, often with such an interlinking of events as could never enter the mind of the present-day physiologist and which *could scarcely be called into existence by means of the technical resources at our command.* Clinical observation will consequently always remain a rich mine of physiologic facts."

In the field of endocrinology clinicians also found that physiologists had "fruitlessly endeavored for decades" to create a solid foundation for functional phenomena so obviously merged with morbid manifestations observed on all sides. They reverted, therefore, to the labors of men in their own field as starting-points of their own investigations: Addison (1849) for the adrenals;

* All italics are my own.

Reverdin (1882), Kocher (1883), Möbius (1886) and Murray (1891) for the thyroid; Pineles (1904) and MacCallum (1912) for the parathyroids; Paltauf (1891) and Bourneville (1900) for the thymus; Langerhans (1869), Laguesse (1893), Minkowsky and Mehring (1898), Lépine (1898) and Opie (1900) for the pancreas; Pierre Marie (1886), Launois and Roy, Fröhlich and Cushing for the pituitary, and many others, all of whom initiated questions which the labors of a multitude of investigators, both in the clinic and in the clinical laboratory, have served to bring to fruition as well-grounded endocrinologic entities. Hence the splendid results attained in our knowledge of the diseases of the endocrines *per se* and in their successful treatment, medical and surgical. It is not here that chaos reigns, however, but in the bearing of the endocrines upon general diseases and their treatment—precisely where the crying need for elucidation is greatest and where death still stalks unhampered in many directions.

Over three decades ago I realized as editor of the *Annual of the Universal Medical Sciences* that medicine as a whole was sodden—as it is still—with discrepancies and gaps which some general fundamental factor seemed alone capable of filling. While twelve years' (1880 to 1891) clinical work at Jefferson College Hospital (which included cases of goiter and exophthalmic goiter) had suggested the ductless glands as candidates for research, physiology proved of incalculable value in the independent analysis subsequently undertaken.

The effort made to fill at least some of the gaps found meant prolonged researches, both in the laboratory and in literature, utilizing, in so far as the latter was concerned, only data which had been confirmed, though giving also due consideration to those which seemed discordant. The method adopted was a novel one, in the sense that all subdivisions of science bearing directly or indirectly upon the solutions sought were utilized, all laboratory or clinical researches required and within my reach being carried out after the contributions of literature had been collected, coördinated, analyzed and then synthetized according to their mutual relationships. Thus data from zoölogy, histology, physiology, pathology, pharmacology, biologic chemistry, clinical medicine, surgery, etc., were used in the upbuilding of each subdivision of the subject studied, the postulate or conclusion reached representing, as it were, a mosaic of all knowledge available on the subject. Discordant data often proved not to be such, for if based on solid observation they usually found in the other branches of knowledge one or more links or connections which converted them into valuable assets. This plan not only avoided theorizing, since the conclusion reached was the end-product of a large number of data from varied sources, but it revealed also erroneous data owing to their inability to fit anywhere.

The conclusions reached and what data a book could accommodate were presented in my work on the *Internal Secretions and the Principles of Medicine*,* the first volume of which appeared in 1903 and the second in 1907. It introduced what appeared to me, at least, a promising outlook for more rapid advance in medical knowledge, for the ductless glands, interpreted from my viewpoint, seemed to fill many of the discrepancies and gaps which both clinical medicine and therapeutics had shown. Swale Vincent clearly outlined the scope of the work when he wrote,[12] "Sajous apparently postulates a relationship between all the ductless glands, whose functions, according to this writer, dominate most of the bodily activities, normal and pathologic." It was, I might add, the first effort of its kind.

That the plan was a sound one is shown by the fact that although the physiologists have failed, during the nineteen years elapsed since it was carried out, to reveal, for instance, the functions of the adrenals—and this applies to other organs—the many data which their labors have accumulated upon this question, and which proved useless to them, have contributed all along to the support of my original conception of these functions. Among the cardinal functions which had remained *sub judice*, and which, from my viewpoint, this method has served to explain, is that of respiration. Its analysis will serve as an example of the value of the mode of research described in the study of obscure problems.

Pulmonary and Tissue Respiration as an Endocrine Function. The respiratory process as now taught in our schools, and despite its vast importance in all diseases, has been known to be defective for over sixty years (Vulpian,[13] Paul Bert,[14] Barnes,[15] Laulanié[16] and others). Briefly the prevailing diffusion theory was found unable to account for oxygen tensions in the arterial blood exceeding those in the air of the lungs; nor for the absorption by the venous blood of all oxygen in the pulmonary air in strangulated or asphyxiated animals; nor for respiration in the greatly reduced oxygen of high altitudes (Bohr,[17] Haldane and Lorrain Smith,[18] Harley[19] and Pembrey[20]). As Bohr pointed out in 1891, and other physiologists have since held, a substance having greater avidity than blood itself was necessary to explain the respiratory process.

In 1903 I submitted that the substance sought was the secretion of the adrenals. The work included besides the analysis of the literature of the subject, laboratory studies of the respiratory system in the lower forms, including insects, crustaceans, mollusks, fishes, batrachians, etc., ascending the phylogenetic scale to man, also of the biochemical reactions of fluids connected with the respiratory process; of the anatomic relations of the organs exposed to

* These words are italicized to emphasize the purpose of the work from the start, *i. e.*, the relationship between the endocrines and the practice of medicine proper.

oxygen-containing media; and finally clinical observations. All of these, including data from literature when coördinated and analyzed, pointed clearly to the adrenals, particularly in view of the marked reducing power of fresh adrenal extracts (Vulpian,[21] Cybulski,[22] Langlois[23] and others) as capable of carrying on the respiratory process.

Since then it may be said that every general feature of the respiratory process, as I interpreted it originally, both pulmonary and systemic, has been confirmed. Adrenalin has been found experimentally to facilitate the free circulation of air in the pulmonary air cells by causing dilatation of the bronchioles (Menten,[24] Jackson,[25] Dixon[26]). It is capable of converting venous blood into arterial blood on exposure to the air and of converting hemoglobin into oxyhemoglobin (Kariya and Tanaka,[27] Menten and Crile,[28] Menten[29]). It increases the intake of oxygen, the output of carbon dioxide, the volume of air breathed, the respiratory excursions of the lungs and the depth and rate of respiration (Byelaventz,[30] Berstein and Falta,[31] Menten,[32] Tompkins, Sturgis and Wearn,[33] Sandiford,[34] Januschke and Pollak,[35] and Nice, Rock and Courtright[36]).

As regards its systemic effects, we have just seen that adrenalin can convert hemoglobin into oxyhemoglobin. In keeping with this observation adrenalin has been found in the blood and red corpuscles (Mulon,[37] Battelli[38]). It takes an active part in tissue oxidation, *i. e.*, cellular metabolism, as shown by many facts. Thus it raises the temperature even in small doses (Oliver and Schäfer,[39] Morel,[40] Lépine[41]) while accelerating metabolism (Reichert[42]). Large adrenal grafts also raise the temperature sufficiently, in some instances, irrespective of any infection, to have caused death (Courmont,[43] Bra[44] and Jaboulay[45]). Even malignant adrenal tumors, regardless of histologic structure, run a febrile course irrespective of any fever causing complication (Israel[46]). As small a dose as 0.5 cc. of adrenalin in 73 experiments in endocrine patients caused an increase in the basal metabolism rate (Sandiford[47]). It causes an increase in the intake of oxygen and in the output of carbon dioxide before accelerating the metabolic rate (Tompkins, Sturgis and Wearn[48]). Moreover, adrenalin in appropriate doses increases the excretion of urea (Addis, Barnett and Shevky[49]).

As controlling evidence, removal of both adrenals should be followed by the opposite phenomena. Briefly it should reduce both the intake of oxygen and the output of carbon dioxide, cause dyspnea, lower the temperature and the metabolic rate, cause myasthenia through slowed muscular metabolism and relaxation of the cardiovascular musculature. That such is the case has been known ever since the time of Brown-Séquard. More precise methods being available the basal metabolism rate has been found

markedly lowered after the operation (Aub, Forman and Bright[50]) and the urea excretion likewise (Bovier and Shevky.[51])*

If facts count at all these few data—which represent but a fraction of those collected and which cover but a small part of the process—should prove convincing in these days when experimentation, a single experiment sometimes, is thought to decide a question. They should mean much when, realizing that tissue oxidation takes part in every morbid process, general or local, we are brought face to face with Halliburton's statement,[54] which corresponds with others that could be quoted, in the last edition of his text-book of *Physiology*, "Our knowledge of tissue respiration is so scanty that we can say little about its pathologic bearing."

The Endocrines in the Genesis of Fever. Turning to the practical bearing of the function of tissue oxidation, as explained, we are brought to realize that the same obscurity reigns concerning its corollary, fever, notwithstanding its preponderating importance in disease. As stated by Lazarus Barlow[55] eighteen years ago, "Even if we grant that fever is beneficial we are completely ignorant of the manner in which it acts." Present-day text-books speak in the same vein. Analysis of the question, however, again confirms the correctness of the explanation of this process I submitted many years ago. MacCallum,[56] for instance, in his recent text-book refers to Rolly and Meltzer, Loewy and Richter, Fukahara and others as having found that if animals were kept at high temperature in a thermostat room they were able to develop a much more effective defence against intoxication and infection than those left outside at ordinary temperatures. If small doses of bacteria or toxin were injected at intervals, "The heated animals showed a great advantage over the controls. They lived longer and many of them survived doses which inevitably killed the control animals." Yet no explanation of the manner in which this phenomenon is produced is vouchsafed.

It may be accounted for, however, by the simultaneous action of several ductless glands. We have seen that adrenalin, when produced in excess, raises the temperature; but so does the thyroid secretion which also, as in fever, first breaks down fats. I submitted in 1903-1907 that both glands took part in the process, the thyroid hormone by increasing the lability of the phosphorus in all nuclei (which all contain organic iodin, as shown by Justus[57]) beginning with those of the fat cells, to the action of the oxygen carried to the tissues by the adrenalin-laden oxyhemoglobin, heat being liberated in the process. I urged also, as had Metchnikoff in respect to phagocytes, that the bacteriolytic and antitoxic pro-

* Suggestive in this connection is the fact that while in 1903 German reviewers[52] characterized tissue oxidation as the outstanding feature of my labors on the adrenals, Weil,[53] in his recent (1921) book on the endocrines concludes that these organs are directly concerned with oxidation.

cess in the plasma was due to a trypsic enzyme which Abderhalden subsequently termed "defensive ferment," bacteria, toxins and other poisons susceptible to its action, being digested by them much as they were in the intestinal canal.* As all biochemists know, however, digestive enzymes are active according to the temperature to which they are subjected, the laboratory maximum temperature of trypsin being about 104° F. This accounts for the fact that heat, whether endogenous, as produced by the interaction of thyroid, the adrenal hormone and the phosphorus of nuclei, nucleoli, etc., or exogenous, as developed in a thermostat, increases the efficiency of the body defences, the purpose of fever.

How is the process governed? MacCallum states in this connection, "As to the nature of the regulating centers nothing is known," but he also remarks, referring to a possible nervous control, "It appears that destruction or interruption of the hypothalamic region of the midbrain throws out of function the regulatory mechanism so that the warm-blooded animal becomes poikilothermic and makes no response to the usual causes of fever." Again has time sustained my personal views—reached by means of the analytic method described—submitted years ago,[58] which showed that while removal of the cerebrum from the midbrain did not prevent the genesis of fever or even the action of antipyretics, sufficient interruption of impulses through a nerve path leading from the pituitary to the thyroid and adrenals did so. Papers by Roussy and Camus, Houssay and others have more recently emphasized its presence by showing that tumors located in this region produced—doubtless by similarly blocking the path—evoked all the phenomena of pituitary insufficiency, polyuria, obesity, tardy development, etc. As illustrated in a colored plate forming the frontispiece of all ten editions of my treatise on the internal secretions, this path passes upward from the pituitary body to the tuber cinereum, thence along the basal tissues to the bulb and cord, and emerges to meet the thoracic sympathetic, the lowest branch entering this system, to pass below and enter the splanchnic nerve on its way to the adrenals—about the level of the third dorsal vertebra—a location recently confirmed by Stewart and Rogoff[59] by means of cross-sections of the spinal cord. On the whole it

* As Mendel (Jour. Am. Med. Assn., March 24, 1906) states: "Enzymes are no longer thought of exclusively as agents of the digestive apparatus; they enter everywhere into the manifold activities of cells in almost every feature of metabolism." This applies also to plant physiology, "all known proteolytic enzymes of plants," as stated by Vines (Ann. Botany, 1901, **15**, 572), "being trypsic." The main active bactericidal agent of phagocytes has been identified by Metchnikoff, Bordet and others as trypsin; this ferment has also been found to digest bacteria in the intestinal canal by Charrin and Levaditi, Zaremba and others. Vaughan also states that "the cell which can no longer supply a digestive ferment is already dead," while Opie clearly associates digestive ferments with the defensive functions of the body when he says that "the ability of the blood to remove injurious material is dependent on the possession of proteolytic enzymes."

would seem as if I had been justified in concluding many years ago that the regulating center of the febrile process was located in the pituitary body and that its influence on fever was exerted through a nerve path governing the functional activity of the thyroparathyroid apparatus* and the adrenals.

All this exemplifies the beneficial side of the endocrine glands, the adrenal, thyroid and pancreatic internal secretions and the pituitary body (the latter only as a coördinating mechanism) coöperating in defending the body against disease.

The Endocrines in the Genesis of Hyperthermia and Autolysis. The prevailing obscurity concerning the nature of three kindred factors, tissue oxidation, fever and the role of the enzymes in the latter, is in my opinion responsible for a large proportion of untimely deaths. From the fact that the underlying cause of temperature production, oxidation, is unknown, it is obvious that the fluctuations of temperature, hypothermia and hyperthermia or pyrexia are likewise. In the light of the foregoing interpretations, however, these phenomena can be accounted for. Reserving hypothermia for the next section we will take up the effects of excessive temperature.

We have seen that adrenal grafts may raise the temperature to such a degree as to cause death irrespective of any infection. Hyperthyroidism may likewise cause a marked elevation of temperature, 110° F., for instance, as in a case observed by Rendu.[62] All clinicians know that danger threatens when 105° F. is exceeded. Below this limit, normal fever is the expression of active but safe defence; the trypsic enzyme then limits its proteolytic action, both in the phagocytes and in the blood, to the pathogenic organisms, toxins, etc., present. When, however, this temperature is surpassed the structures in immediate contact with the blood or within it are first exposed to the digestive process of the "defensive" ferment, the red corpuscles yielding first (hemolysis), then the cardiovascular endothelium, the serous membranes, peritoneal, pleural, pericardial, meningeal, etc. (autolysis), according in a measure to the virulence of the pathogenic agent as an antigen and the local vascular supply.

Valvular lesions, for instance, are now attributed to the direct action of the pathogenic bacteria themselves, but this has never been demonstrated. If it were true, how account for their production by Christian and Walker[63] with uranium nitrate, potassium bichromate, arsenic in various forms, spartein and adrenalin

* The protective influence of this apparatus against certain infections has been confirmed in various ways. Lévi and Rothschild[60] write in this connection: "Sajous has attributed among the functions of the thyroid body a role which he assimilates to that of opsonins and autoantitoxins. Fassin, Stepanoff and Marbé have all confirmed the influence of the thyroid on the blood's asset in alexins and opsonins." The two latter investigations were conducted at the Pasteur Institute of Paris. Col. McCarrison[61] also concluded after experiments that "the thyroid gland contributes largely to the body's antitoxic and bactericidal functions."

given in succession? All these drugs, as I have shown elsewhere,[67] are capable, either directly or indirectly, of enhancing the functional activity of the pancreas,* and also by promoting a reaction of the adrenals and thyroid, thus accelerating tissue oxygenation and increasing the lability of the cellular nucleins, raise the proteolytic activity of the trypsin. The soundness of this conception is suggested by MacCallum's statements that "this liquefaction by means of a proteolytic ferment is exactly the process known as autolysis, except that it is recognized in that process that all tissues can tolerate in varying degrees of intensity the proteolytic ferment to dissolve their own cell bodies." He also refers to Dernby[68] as having shown that "in all tissues studied there are both pepsin-like and trypsin-like enzymes, etc." That hyperthermia by raising the digestive activity of these enzymes will tend to destroy the tissues containing them is self-evident.

The pathologic field covered by this greatly simplified conception of a very complex subject is almost bewildering. Cardiovascular diseases, particularly those of inflammatory origin and their complications, cause the bulk of our mortality; it has now exceeded, according to the international list of the 1914 Census, those of tuberculosis and pneumonia. Both of the latter great killers of mankind can also be shown to owe their great mortality in part to autolysis in most instances. We have seen that this applies also to the acute diseases of serous membranes, the pleura, peritoneum, etc. In various gastric, intestinal, pancreatic and hepatic diseases where contact with ferments prevails autolysis is a common source of lesions; typhoid, appendicular and colonic ulcerations are examples of its effects. The whole cerebrospinal system is subject to autolysis, as attested in part by the scleroses and the paralyses they entail. This list, which could be greatly extended, sufficiently illustrates the importance of hyperthermia and autolysis in pathogenesis.

Here again we find the endocrine glands taking an active part in disease, but as morbific agents. The same organs, the adrenals, the thyroid and the pancreas impelled to excessive efficiency by a profound toxemia, destroy not only the pathogenic agency whatever it be, but also the affected tissues and often life itself.

Cardiac Failure of Endocrine Origin as a Cause of Death. While the adrenal secretion sustains pulmonary respiration and tissue oxidation, certain structures, the sympathetic system (whose ganglia and nerves contain the adrenal medullary principle) and the involuntary smooth muscular fibers, as shown by Oliver and

* The prevailing idea, due to Eppinger, Falta and Rudinger, that adrenalin inhibits the pancreas, is due to an experimental error. As stated by Sollmann,[64] "the theory is not based on good evidence." MacCallum[65] also denies its correctness. R. G. Hoskins[66] has recently also condemned it.

Schäfer,* the heart, the arterioles, and through the latter the muscular coats of the stomach, intestines, etc., are especially sensitive to its action. All these structures, therefore, are the first to feel the effects of excessive or deficient secretory activity of the adrenals. This selective effect is often an underlying cause of death due to adrenalin administered early in the course of anesthesia. Both chloroform (Aloi) and ether (Marchette) causing abnormal activity of the adrenals at first, the excess of adrenalin in the blood plus the adrenalin injected provoke such violent constriction of the arterioles that the sudden increase of vascular tension produced behind these terminal vessels causes cardiac arrest. Administered later, however, if cardiac failure occurs, adrenalin is very efficient because the adrenals have themselves become insufficient through the excessive secretory activity of the first and second stages. Preoperative injections of adrenalin in robust subjects have also caused death by adding an excess of adrenalin to the already abundant residual supply. Fear, excitement, anger, etc., may also prove lethal by inducing, doubtless in keeping with Cannon's theory, excessive secretory activity of the adrenals. Yet all these morbid effects are produced indirectly.

Far more frequently encountered in practice, however, is the condition previously referred to: That known generally as "adrenal insufficiency," and which I have termed "hypoadrenia." Quite in accord with the functions of the adrenals described its general symptomatology, subject to variations according to the causative condition, is briefly: Asthenia, great muscular weakness, extreme sensitiveness to cold, cold extremities, hypotension, weak cardiac action and weak pulse; anorexia, slowed basal metabolism rate, constipation and psychasthenia. Many of the perambulating cases of so-called idiopathic anemia are due to hypoadrenia, the pallor being mainly the result of vascular torpor and recession of the blood mass from the periphery to the splanchnic area.

The death-dealing influence of hypoadrenia manifests itself especially among the elderly. Histologic and vascular injection studies have conclusively shown that atrophy of the adrenals progresses steadily as age advances. Their vascular supply in a man of eighty years is hardly one-third that in one of thirty years—a condition which also prevails in the other endocrines. When, therefore, an infection strikes such a subject the defensive powers are such as to give it greater sway than in younger individuals, and the mortality is correspondingly greater.

A striking example of this condition is senile pneumonia which Charcot characterized as "the great enemy of old people." Refer-

* My conception of the function of the adrenals sustains their theory, also the antitoxic theory of Abelous and Langlois and the emergency theory of Cannon, all of which, as stated, are normal manifestations of the fundamental function I attribute to these organs.

ring to its high mortality in subjects over sixty years of age, Osler also states, "From the reports of its fatality in some places one may say that to die of pneumonia is almost the natural end of old people." It may occur and prove fatal suddenly and unexpectedly right in the midst of the victims' occupations. Where, however, as in most instances, the disease develops gradually the symptoms are typical of failure, more or less rapid, of the adrenal functions. After a brief reaction to the infection, slight fever, very moderate rise of blood-pressure, no chill other than perhaps a chilly sensation, little if any cough and expectoration and no pain in the chest, there occurs, as Elsner[69] well described it, "rapid lowering of the arterial tension, marked lividity, edema of the lungs and extreme asthenia"—all typical signs of adrenal failure. As shown by Oliver and Schäfer in 1894, the adrenal secretion on its way to the lungs sustains the contractile power of the right heart. Elsner states that "dilatation of the heart, particularly of the right side, is a frequent complication of senile pneumonia"; he also records a fact of cardinal importance in the present connection, *e. g.*, that the dilatation of the right heart "sometimes *precedes* the infection," which means that the latter may be secondary to the adrenal failure.

Practically all acute infections may lead to a condition of the adrenals similar to that in senile pneumonia. It may supervene in lobar pneumonia at any age, in bronchopneumonia, typhoid fever, diphtheria, scarlatina, erysipelas, septicemia and in severe cases of measles, mumps and acute peritonitis—in a word, in all infections in which the febrile reaction is severe and prolonged. During the active early febrile process the adrenals, as shown in the section on the genesis of fever, secrete actively to carry on their part in the defensive function. Sooner or later, however, their efficiency weakens and the secretion produced is insufficient to carry on tissue oxidation and sustain the heart. This condition, which I have termed "terminal hypoadrenia," owing to its occurrence after the acute symptoms have ceased, gives rise to signs which differ but little if at all from those observed in senile pneumonia: Extreme lassitude, low blood-pressure, subnormal temperature, weak and rapid pulse, more or less dilatation of the heart and tendency to faint.

Terminal hypoadrenia thus illustrates a direct connection between the adrenals and a large number of general diseases. It also indicates that although functionally related with other ductless glands, the thyroid, pancreas, pituitary, etc., the adrenals are the most important organs of the endocrine group as far as symptomatology is concerned.

Therapeutic Control of Endocrine Functions. Molière, in his *Bourgeois Gentilhomme*, makes his candidate for patrician rank marvel at the fact that he had all his life been using prose. This

applies in a measure to the control of endocrine functions, which physicians have learned to do without realizing it. Thus the agents probably most used in practice today, the iodides, are now known to owe this property to the fact that their iodin is taken up by the thyroid gland to build up its secretion. I pointed this out in 1907,[70] and Marine and Williams[71] showed that the proportion of these salts taken up by the organ was constant in normal glands, but that this varied with the degree of hyperplasia present. Whether administered pure, as a salt, as a glandular product, or as Kendall's thyroxin matters not: The gland appropriates just what it needs, and, as this varies greatly with each patient, the initial dose should always be small.

Another agent in common use is strychnin: I urged in 1907[72] that this salt stimulated the adrenals. This was confirmed by Stewart and Rogoff[73] in 1919, who found that ordinary doses caused a marked and lasting increase in the production of adrenal secretion. When we recall that the adrenal principle is present in all sympathetic ganglia and nerves (and, according to my researches, in the axis-cylinders and cell bodies of all nerve cells, cerebrospinal and peripheral) we can well understand the almost ubiquitous use of strychnin by neurologists in atonic functional disorders. The same action, but to a less marked degree, obtains in the case of nux vomica and brucine.

Still another group is that represented by digitalis. Traube in 1871 showed that section of the spinal cord high up annulled the effects of digitalis, while Boehm[74] found that this procedure also arrested the effects of digitalis when they had become manifest. We have seen that, from my viewpoint, there is a nerve path from the pituitary *via* the basal tissues, cord and splanchnic to the adrenals. In 1917[75] I submitted that it was by stimulating the adrenals that digitalis produced its effects on the heart. In 1915 H. N. Richards and W. G. Wood[76] found that both digitoxin and strophanthin stimulated the "central nervous mechanism controlling the secretion of the suprarenal glands," and that this ceases "after section of the splanchnic nerves or of the spinal cord between the fourth and fifth cervical nerves," the section thus severing the path referred to above. Apocynum, convallaria majalis and spartein, from my viewpoint, act similarly upon the adrenals, though less actively than digitalis.*

The action of the adrenal secretion upon cardiac tone, first shown by Oliver and Schäfer, is well known. Yet if the digitalis group actually affect the heart through the adrenals interruption

* The London Lancet of September 25, 1920, editorially recommended the study of this phase of therapeutics, which I had termed "pharmacoendocrine therapy," by pharmacologic authorities when a committee appointed by the Minister of Health of Great Britain on the standardization of endocrine products would have finished its report.

of the secretion of the latter should impair its action. Stewart and Rogoff[77] found that compression of the adrenal veins, which carry the adrenal secretion to the inferior vena cava, the venous blood of which in turn takes it to the heart, caused arrhythmia, but that the heart resumed its normal action when the veins were released.

These few main agents suffice to indicate that the thyroid and adrenals can be stimulated by familiar remedies. Yet how account for this common action on the adrenals when the various drugs mentioned produce, as we all know, dissimilar pharmacologic effects? We have seen that the function of the adrenals is to carry on pulmonary and tissue respiration. Now, all adrenal stimulants, strychnin, digitalis, alcohol, ether, chloroform, caffein, nicotine, turpentine, etc., as shown by well-grounded researches, increase respiration, but only in small doses, which vary considerably with each agent, and beyond which doses toxic phenomena appear. But they also produce other effects; they may act on the vasomotor center, the reflexes, the excretory organs, etc. Briefly, each drug is endowed with its own specific characters because of the variety of incidental effects it may produce. It is only when its stimulating action on the adrenals overtops all other effects that the specific phenomena due to this organ manifest themselves.

Organotherapy coöperates advantageously and on rational lines in this connection by increasing greatly the efficiency of the stimulating drugs used. Wherever there is hypothyroidea, thyroid gland alone is often efficient, but it becomes especially so if suprarenal gland and strychnin are also given, because hypoadrenia is likewise present. Strychnin by stimulating the adrenals causes them to appropriate the suprarenal gland administered more rapidly and to increase the metabolic rate earlier than when either agent is administered alone. Again, the heart failure of the aged fails totally at times to respond to digitalis, strychnin or any other agent. But the concomitant use of suprarenal gland to feed their atrophied adrenals soon changes the picture and will sustain the heart if persisted in. In senile pneumonia the very slow injection of seven minims of the 1–1000 adrenalin solution in a syringeful of saline solution administered intramuscularly every three hours is a powerful adjunct to the other measures used. This applies also to the cardiac failure or terminal hypoadrenia of all acute infections. Its power to save life under these conditions is striking. In chlorosis and other anemias in which iron is indicated the addition of suprarenal gland—provided it be active—favors the formation of hemoglobin, of which both it and the iron are constituents. These are, of course, but a few of a large number of our trusted remedies to which organic products become powerful helpmates.

Recalling the genesis of fever, we have seen that the digestive tryptic ferment owes its bacteriolytic and antitoxic activity to the liberation of heat through the coöperation of the thyroid and adrenal hormones and the cellular nucleins. Thus explained, the process accounts for several hitherto obscure effects, the therapeutic action of the heat, for instance, in its many forms. Heliotherapy is one of these. C. W. Saleeby,[78] in suggesting its study to the British Medical Research Council, credits Sonne, of Copenhagen, with the view that curative effect "is due to the capacity of the luminous rays during the light bath, to heat a very essential portion of the aggregate blood volume of the organism to a temperature possibly exceeding the highest fever temperature ever measured without causing the body temperature to rise to any appreciable degree." This deep penetration of sunlight harmonizes well with my conception of fever. Heliotherapy thus acts by supplying the tryptic defensive enzyme with the heat energy necessary to raise its bacteriolytic efficiency to its highest level, the adrenals and thyroid of the tuberculous child having acquired or inherited its liability to infection mainly through insufficiency of these two organs which manifests itself by inadequate development of heat energy. The vesperal fever is a protective reaction due to partial recuperation of the endocrines during the intervals. The beneficial effects of iodin early in tuberculosis are also explained, since it contributes to the heat-generating process while sensitizing the tubercle bacilli to the proteolytic action of trypsin.

Hyperthermia or pyrexia with all its dangers has also been met by the right measures: cold baths, even though their mode of action has not been understood. Briefly, by reducing the actual temperature through heat dissipation, the proteolytic activity of the defensive trypsin is antagonized. This explains also why the so-called "antipyretics" proved apparently so only, while in reality increasing the chances of death. After a primary stage of peripheral hyperemia they caused constriction of the arterioles, thus interfering with heat dissipation; in this manner they actually favored heat accumulation in the deeper tissues while the peripheral circulation was sufficiently embarrassed often as to cause cyanosis with formation of methemoglobin.

Another life-saving measure in addition to cold baths and other hydropathic uses of cold is the free use of saline solution with sodium bicarbonate added thereto in the proportion of 1 dram to 1 pint. It may be used as a pleasant beverage, equal parts with milk being ordered several times a day. By sustaining the osmotic properties of the blood and preventing abnormal viscidity and also acidosis, the kidneys are protected and the chances of both pyrexia and autolysis are materially reduced. The colonic use of saline solution and hypodermoclysis are also efficient in this direction.

Examples of the direct inhibitive control of the endocrines or

their effects are numerous. The use of quinin hydrobromide and ergotin in exophthalmic goiter, so effective in conjunction with rest, etc., is based upon its controlling influence upon the vascular supply of the thyroid, the adrenals and the thymus. The functions of an organ depending upon the proportion of arterial blood it receives, as shown by Claude Bernard, the functional activity of these glands is reduced correspondingly. The salicylates influence the endocrines in the same way. Arsenic is a potent agent in this direction. It inhibits, by a central action, the production of both the thyroid and adrenal hormones, and, as Cushny states, "lessens oxidation in the tissues," and therefore the results of abnormal proteolysis of the blood elements. Hence its great value in pernicious anemia.

One more example among the many which could be submitted is the direct antagonistic action of the nitrites to the constrictive action of the adrenal secretion upon the arterioles. Sollmann,[79] for instance, though unaware of their controlling influence over the suprarenal phenomenon, writes, "The fall of blood-pressure is due entirely to the extensive vasodilatation produced by the direct action of the nitrite on the arterioles." A life-saving measure suggests itself in this connection for cases such as those previously mentioned, in which adrenalin used early in the course of chloroform or ether anesthesia is added to the excess due to the adrenal stimulation caused by these anesthetics, tends to arrest the heart, viz., inhalations of amyl nitrite, which at once dilate the arterioles.

Conclusions. Why is the "endocrinology" of today in such a chaotic state? We have seen that the underlying cause is the prevailing obscurity concerning the physiologic functions of the endocrines. But Sir James Mackenzie[80] also wrote recently: "The conception of medical research which is dominant today is so immature and imperfect that it renders fruitless much of the research work. Indeed, so imperfect is the conception that fields essential to medical progress are not recognized." I might add that millions of dollars are being wasted on sterile researches and as many lives compromised through this arbitrary negation of newer fields simply because they do not appear to fit in with beaten though sterile paths.

While the foregoing study tends to sustain Mackenzie's criticism, it also affords evidence based on nearly twenty years' test to the effect that there is available a way of turning the tide. This is, as I have long urged, to *give the endocrines their due as major organs* as important as any other in the body and to realize that *they are mainly concerned with the preservation of life* though capable, *when functionally overactive, of causing death.* This has been exemplified by showing their participation in functions which, notwithstanding their overwhelming importance and much labor, had remained

obscure. There are over ninety other great problems* quite as obscure and quite as important to human welfare which the endocrines can solve in conjunction with available data from all other branches of medical science.

Interpreted from my viewpoint, endocrinology imposes no sacrifice of what we know; it is eminently constructive in the sense that by filling gaps in all directions it finally solves problems of various kinds which, although near solution for decades, lacked precisely what the endocrines furnish to bring them to fruition. We have seen that the adrenals fill this role in pulmonary and tissue respiration, a cardinal physiologic function which had virtually remained *sub judice* six decades. We have seen also what the endocrines contributed to pathology by explaining four additional questions of the first importance, fever, pyrexia, hemolysis and terminal heart failure. As to therapeutics, the endocrines are fruitful in practically every phase of the subject studied as illustrated by the twenty and odd drugs and other remedial measures analyzed. Moreover, their study herein must have afforded some degree of surprise to the ultraconservatives referred to at the beginning of this address, by causing them to realize that they had all along been endocrinologists . . . but of the right kind. Their spirit of fairness should suggest, however, in view of the fact that they have so far been using the drugs and measures reviewed empirically, that the endocrines bid fair to place therapeutics on a scientific footing. Indeed, it looks as if it might in the end furnish medicine as a whole, and as a reward for the vast labor its development has imposed upon workers in all its branches, the last link it needed to place it upon the highest plane of efficiency.

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* The list of these leading features, ninety-six, was published in the introduction of the first eight editions, on page xii in the second volume of the first two editions and on the same page in the first volume of the following six editions of Internal Secretions. Despite the many years elapsed since they were first written the fundamental principles outlined would be subject to but few changes today if analyzed by the system described in the present paper.

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A RÉSUMÉ OF OUR KNOWLEDGE OF THE FUNCTIONS AND INTERRELATIONS OF THE ENDOCRINE GLANDS.*

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and

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This report is based upon a review of recent literature, together with an examination of a number of recent works upon the endocrine glands.†

In the preparation of this review we have endeavored to include only those contributions which on investigation appeared to have either sound clinical or experimental foundations, excluding as far as possible all unreliable, fantastic and purely hypothetic material, in which the literature unfortunately abounds.

To follow a definite plan in the presentation of the data relating to each gland has been found impossible, because of our failure to find sufficient reliable material relating to some of them.

The first significant conclusion reached in the study of these organs is the apparent fact that each possesses a definite period of activity during which it appears to exert powerful metabolic influences over various portions of the organisms.

With this thought in mind, Walter Timme,[1] in a recent article, happily groups the internal secretory glandular system by dividing mankind, endocrinologically speaking, into three epochal periods: The first, presided over chiefly by the thymus and the pineal, embracing the span of years from birth to puberty (period of growth and development); and second, between puberty and prime (years of aggression, activity and reproduction) is under the domain of the gonads, whose control is, however, greatly assisted and considerably modified both here and in the later portion of the first period by the thyroid, the pituitary and the adrenals; and the third, the period of general deterioration (involution to dissolution), marked by gradual diminution in the activity of the whole endocrine system.

The Thyroid Gland. Concerning the thyroid gland we find that while all authorities admit the powerful influence of this organ on general metabolic processes, and while it is generally supposed that the iodine-colloid constituent of the thyroid gland is its specific secretion, nevertheless there is no conclusive data by which the presence of a specific autocoid can be assigned to this gland, in spite

* Read before the West Branch of the Philadelphia County Medical Society, February 14, 1922.

† Complete bibliography omitted, only direct references will be found in the article.

[1] Neur. Bull., 1921, **1**, 83.

of the splendid work of E. C. Kendall,[2] who has succeeded in isolating from the non-protein iodine-colloid of the thyroid a pure crystalline substance of constant composition containing over 60 per cent of iodine, which has been called thyroxin, and which he believes to be the active constituent of this gland. As to whether this iodine-containing material is manufactured within the gland itself or whether the thyroid simply acts as a storehouse for iodine for the rest of the body has not been determined, Falta[3] and Kraus holding opposing views.

Ardent exponents of the *interrelation* of the glands of internal secretion have gone so far as to suggest thyroidectomy for the relief of diabetes mellitus where associated with evident thyroid hyperfunction. This pernicious theory is opposed by Fitz,[4] who reports 39 cases of diabetes mellitus associated with hyperthyroidism in whom thyroidectomy and the roentgen-ray failed to influence the glycosuria to any appreciable degree or for any reasonable length of time.

Thyroid to Parathyroid. A reciprocal function between the thyroid and the parathyroids was first suggested by Vincent and Jolly[5] after their experimental demonstration of hypertrophy of the parathyroids and the appearance of colloid material between their cells after removal of the thyroid. Blair Bell does not wholly concur in this view, while Macleod[6] has gone so far as to assign entirely distinct functions to the thyroid and the parathyroids. This opinion being based, in part at least, upon the work of Paton and Findlay,[7] who present evidence to show that the parathyroids exert their action mainly on and through the nerve centers, while the thyroid exerts its function primarily on metabolic processes through the blood stream. More recently Vincent and Arnason[8] have reinvestigated this problem without finding any experimental evidence to support Vincent's previous view that the parathyroids remaining after thyroidectomy become hypertrophied or develop characteristics of thyroid tissue.

Thyroid to Pituitary. An intimate relationship between the thyroid gland and the pituitary is generally accepted. This is shown by (*a*) the formation of colloid masses, not normally present in the pituitary, following thyroidectomy, this colloid assuming the same staining characteristics as the thyroid colloid; (*b*) the similarity of the structural changes occurring in diseases of the thyroid and of the pituitary; (*c*) the observation of Bell and others that removal of the thyroid increases the secretory activity of all

[2] Med. Clin. North America, 1919, **3**, 3, 583.
[3] The Ductless Glandular Diseases. P. Blakiston's Son Co., 1915.
[4] Arch. Int. Med., March 15, 1921, p. 305.
[5] Jour. Physiol., 1905, **32**, 65; 1906, **34**, 295.
[6] Physiology and Biochemistry, 3d edit., C. V. Mosby Co., 1920.
[7] Quart. Jour. Exper. Physiol., 1916, **10**, 214.
[8] Endocrin., 1920, **4**, 199.

parts of the pituitary; (*d*) the close neurologic relationship as shown experimentally by stimulation of the sympathetic, which causes an increase in secretion of the adrenals, thyroid and pituitary;[9] (*e*) the close embryologic relation of these two glands; the thyroid and the glandular portion of the pituitary both arising from outgrowths of the entoderm lining the floor of the pharynx, where they are closely connected until the third month of embryonic life.

Thyroid to Ovaries. The close physiologic relationship between the thyroid and ovaries has been long known. This is well shown by (*a*) the frequent enlargement of the thyroid at puberty, during pregnancy and at the climateric; (*b*) the prevalence of menstrual disturbances accompanying both hypofunction and hyperfunction of the thyroid; (*c*) by the fact that thyroidectomy is followed by atrophy of the uterus; (*d*) because deficiency of the thyroid in early youth or the removal of the thyroid in early youth or in young animals prevents the normal development of the sex glands. Finally, castration has been shown by Bell and Hick[10] to favorably modify the profound metabolic crisis seen after thyroidectomy.

Thyroid to Suprarenals. Notwithstanding the statement of Bell[11] that in three of his experimental animals he noted an increase in secretory function of the suprarenal cortex following thyroidectomy, we are forced to conclude with Macleod[12] that reliable experimental evidence has so far failed to show any definite relation between the thyroid and the suprarenals.

Thyroid to Thymus. The persistence of the thymus gland in exophthalmic goiter as well as the known anatomic and embryologic relationship of these two glands suggest their close physiologic association, although this has not yet been proven by reliable experimental or physiologic work. (*Vide infra.*)

Comment. Viewed in the light of the foregoing conclusions the question naturally arises: Is there an internal secretion of the thyroid? or does the gland exert its influence on the pituitary, parathyroids, ovaries and thymus through an interrelated nervous mechanism? In this connection some authorities have even gone so far as to question whether even the toxic symptoms of so-called toxic goiter are the result of hypersecretion of the thyroid (Marine and Lenhart[13]).

Opposed to the toxic theory, Macleod[14] cites the following experimental evidence: (*a*) The injection into animals of the blood of patients suffering from thyroid hypersecretion is not followed by evidence of any toxicity characteristic of hyperthyroidism; (*b*)

[9] W. Langdon Brown: The Sympathetic Nervous System in Disease, Henry Frowde, Hodder & Stoughton, Ltd., London, 1920, p. 161.

[10] British Med. Jour., 1909, **1**, 157.

[11] The Sex Complex, William Wood & Co., 1916, p. 54.

[12] Loc. cit., p. 788.

[13] Arch. Int. Med., 1911, **8**, 265.

[14] Loc. cit., 798.

the administration of an extract of a gland removed from an exophthalmic case had no different physiologic action upon a normal animal than an extract from a normal gland containing the same percentage of iodine; (*c*) degenerative and pigmentary changes in the ganglion cells of the cervical sympathetic have been found in cases of exophthalmic goiter and are believed by Wilson[15] to be characteristic of this condition. For these reasons disease of the sympathetic system may well be assigned the etiologic role in the production of the cardiac and ocular symptoms as well as the thyroid hypertrophy secondary to which the metabolic phenomena characteristic of this disease naturally follow.

The Pituitary. It is usually accepted that the anterior lobe of the pituitary gland is chiefly concerned in maintaining and regulating body growth, particularly of the skeletal portion, and in addition entering into the metabolic activity concerned in the establishment of puberty and sexual maturity. The posterior lobe is assumed to be active in the production of a powerful autocoid which is closely concerned with the physiologic activity of unstriped muscle, while the pars intermedia is believed to be associated with the posterior lobe in the production of this autocoid. We have not been able to accept these statements without considerable reservation, since the literature abounds in clinical and experimental evidence which cannot be wholly reconciled to this belief. Thus, Frank,[16] correlating the work of a number of investigations relative to the influence of the pituitary extract to the development of the genital tract, concludes that this substance has not been shown to stimulate the development of the female sex organs, and has very little if any effect upon those of the male.

The most striking thought relating to the modern conception of the functions of this gland comes from Dr. Sajous, who recently stated that there is no reliable evidence to show that the pituitary produces any internal secretion, the statements of many observers and the deductions of Cushing notwithstanding. Sajous supports this revolutionary theory by bringing forward abundant experimental and clinical evidence to show that (*a*) the administration of anterior lobe extract never has been shown to affect the growth of children;[17] [18] (*b*) the anterior part, which is said to be the active agent controlling the histologic growth of the body, presents no microscopic evidence of secretory tissue; (*c*) there has never been any reliable demonstration of a secretion from this lobe; (*d*) the relation of the pituitary to acromegaly cannot be substantiated, since were this affection the result of a perverted

[15] Am. Jour. Med. Sc., 1916, **152**, 799.
[16] Jour. Am. Med. Assn., 1919, **73**, 1764.
[17] R. Klinger: Arch. f. d. ges. Physiol., 1919, **177**, 232.
[18] P. E. Smith: Anat. Record, Philadelphia, 1921, **21**, 83.

secretory activity the results could neither be unilateral nor localized;[19] (*e*) that clinical and experimental evidence shows that pressure on the tuber cinereum produces the same effect as pituitary disease. To this we might add that an extensive study of the effect of pituitary opotherapy in experimental diabetes insipidus by Camus and Roussy,[20] who show that the polyuria usually attributed to a lesion of the pituitary is in reality due to a lesion in the base of the brain. Sajous's present hypothesis is, therefore, that the pituitary organ operates through the agency of a demonstrated nervous relationship by way of the splanchnics, such activity being possible because the posterior pituitary lobe is in reality the main ganglion of the sympathetic, which controls the thyroid, the adrenal and the thymus and coördinates them.

Pituitary to Thyroid and Ovaries. Relationship between the thyroid and pituitary is shown by the fact that the removal of either gland produces strikingly similar effects upon the sexual functions and the general development of young animals, although according to Robertson, Goetsch and others[21] the administration of pituitary extract produces no stimulating effect upon the development of the sex organs, at least in females.

Additional proof is found in the fact that when the condition known as hypopituitarism is experimentally produced the thyroid and thymus glands enlarge, while the cortex of the suprarenals and the sex glands fail to develop. In adults clamping or separation of the stalk results in intense atrophy of the uterus and of the ovaries, while at the same time the thyroid enlarges and its colloid content increases.

Pituitary to Suprarenal. The assumption that there exists a definite relationship between these two glands appears to be based upon the statements of observers, who based their opinion solely upon the supposed similarity of physiologic action of the extracts of the two glands. More recent physiologic experiments question this relationship because it has been shown that pituitary and suprarenal gland extracts are dissimilar in their action; thus pituitrin acts directly upon the involuntary muscle fibers themselves while epinephrin acts solely upon the receptor substance associated with the terminations of the sympathetic nerve fibers in the involuntary muscles.[22] As to a definite endocrine relation, clinical and experimental evidence is generally conflicting. Such authorities as Cushing[23] and Bell[24] take opposite views, the former stating that partial pituitary destruction leads to a definite hyperplasia of the suprarenal, while the latter was unable to demonstrate such an effect.

[19] C. Bellavitis: Abstract Endocrin, 1921, **5**, 653.
[20] Comp. rend. Soc. de Biol., Paris, 1920, **83**, 1578–1583.
[21] Editorial, Jour. Am. Med. Assn., 1917, **69**, 1697.
[22] J. J. R. Macleod: Loc. cit.
[23] The Pituitary Body and its Disorders, 1st edit., J. B. Lippincott Company.
[24] Loc. cit.

Pituitary to Pancreas. Because of the influence of pituitrin upon carbohydrate metabolism, which is thought to be primarily controlled by the islands of Langerhans, effort has been made to establish an endocrine relation between these two glands; thus Kraus[25] states that after removal of the pancreas in cats (*a*) the eosinophil cells of the hypophysis disappear. These cells also disappear in juvenile diabetes; (*b*) the thyroid first hypertrophies and then becomes smaller; (*c*) the lipoid disappears from the cortex of the adrenals while the medulla stains more deeply with chromic acid; (*d*) the gonads and the pineal become smaller and (*e*) the parathyroids show no change; on the other hand many carefully conducted investigations do not corroborate these findings, so that the presence of any endocrine relation is still in doubt.

Pituitary to Parathyroid. Nothing definitely known.

The Suprarenal Glands. *Anatomy and Physiology.* Our knowledge of the suprarenals is most complete, because these organs lend themselves best to methods of experimental study.

The suprarenals are made up of two embryologically independent parts—the external portion, or the cortex, and the internal portion, or the medulla. The intermediary zone belongs to the cortex. The cortex is composed of columns of cells containing highly refractive lipoid granules. The medulla is richly supplied with nerves and multipolar ganglion cells, and in addition nests of cells which take a brown color when stained with chromic acid, because of which they are termed chromaffin cells. This chromaffin tissue is supposed to produce a highly complex compound which is chemically related to albumin, tyrosin and phenylalanin, known as suprarenalin or adrenalin. Experimental study shows that adrenalin acts only on the purely sympathetic nerve-endings, especially on the so-called musculoneural junction.

The important physiologic properties of adrenalin are: (*a*) An ability to elevate blood-pressure by constricting the peripheral vessels without the assistance of the splanchnic innervation;[26] (*b*) inhibition of the musculature of the intestines, the stomach, the esophagus, the gall-bladder, the urinary bladder, also of such glandular structures as the lacrimal, the salivary, the mucous glands of the mouth and pharynx and the gastric glands; (*c*) an accelerator of the three sphincters (the pyloric, the ileocecal and the internal sphincter of the anus); (*d*) glycogenolysis, as shown by the production of glycosuria and hyperglycemia after its intravenous injection, and (*e*) shortening of the clotting time of the blood. It is worthy of note that most of these physiologic activities find their counterpart in the sympathetic and follow experimental stimulation of the sympathetic nerve supply to these organs.

[25] E. J. Kraus: München. med. Wchnschr., 1921, **68**, 794.

[26] W. Loffler: Schweizer Arch. f. Neurol. u. Psych., Zürich, 1921, **8**, 163–184; Abst. Endocrin., 1921, **5**, 803.

This similarity of action between adrenalin and the sympathetic system is explained, on the basis of comparative anatomy and embryology, by the fact that the chromaffin tissue found in the suprarenals originates in an outgrowth of the neuroblast from which is laid down the primitive ganglia of the posterior roots, masses of cells being split off which become the common ancestors of the sympathetic ganglia and the chromaffin system.

Adrenals to the Thyroid and Parathyroid. There is no reliable data to prove a hormonic relationship between the adrenals and the thyroid and the parathyroids, although relationship between the adrenals and thyroid has been asserted, because thyroid feeding is said to produce hypertrophy of adrenals. Opposing this view it has been shown by Gley,[27] Carlson[28] and Stewart and Rogoff[29] that thyroidectomy causes a similar hypertrophy.

Adrenals to the Sex Glands. Embryologically the close relation of the adrenals to the sex glands is well known. Such an association is well supported clinically by the fact that in cases of sexual precocity the adrenal cortex has been shown to be hypertrophied, while certain tumors of the adrenal cortex in young children not producing destruction of the gland are generally associated with premature development of the secondary sexual characteristics. In addition, hypertrophy of the adrenal cortex during pregnancy is an established fact. Furthermore, in hyperplasia of the adrenals changes occur in the testicles, particularly in the interstitial cells, although experimental castration has not been shown to have any constant effect upon the adrenal cortex.

No relationship between the medulla of the adrenals and the sexual organs has yet been established.

The Adrenal to the Pituitary. As already discussed under the head of the pituitary no definite physiologic or hormonic relationship has yet been established between these two glands, although Blair Bell[30] states that after partial removal of the adrenals the pars anterior cells show certain alterations in staining characteristics which he believes indicates an increased activity of the pituitary.

Concerning the other glands of internal secretion we have been unable to find any evidence of correlation with the adrenals.

The metabolic relation of the adrenals is important, as shown by the fact that the injection of epinephrin in normal animals is followed by hyperglycemia and glycosuria. This is explained by the demonstrated ability of epinephrin to convert glycogen into glucose. This glycogenolytic function is believed to be dependent primarily upon the action of the sympathetic mechanism, the

[27] Arch. internat. de physiol., 1914, 14, 175–194.
[28] Jour. Am. Med. Assn., 1916, 67, 1484.
[29] Am. Jour. Physiol., 1921, **5**, 560.
[30] Loc. cit.

normal functional activity of which is maintained only by the presence of a proper concentration of adrenalin in the circulating blood. Additional metabolic activity of this gland is shown by an increase in calcium, phsophorus and urea elimination after experimental removal of one of the adrenals.

The Parathyroids. Embryologically the parathyroids are entodermal glands having a common origin with the thymus from the branchial arches in close association with the origin of the thyroid. The so-called *epithelial bodies* of the parathyroids develop from the dorsal part of the third and fourth branchial pouches.

Functional independence of the parathyroids was for a long time unrecognized because this intimate relation above described permitted these glands to be in direct contact with, or even included within, the body of either the thymus or the thyroid, or both. More recent studies and investigations have demonstrated the individual functional activity of these glands. Paton,[31] for example, claims that complete experimental deficiency of the thyroid does not produce any of the symptoms of tetany, while deficiency of the parathyroids is not made good by thyroid therapy, and finally extirpation of the parathyroids alone disturbs calcium metabolism, with the production of tetany but without the production of myxedema.[32]

There is neither clinical nor experimental evidence to prove the existence of a specific parathyroid hormone. The parathyroids are concerned mainly with exercising a restraining or inhibitory influence over certain nerve centers and in controlling to some degree the calcium metabolism.

Hypoparathyroid activity results in disturbed calcium metabolism accompanied by a loss of calcium from the blood and nervous tissues with the production of tetany.[33]

Sex Glands. Embryologically and anatomically the sex glands of the male are usually separated into two distinct functional parts, *i. e.*, the reproductive portion and the interstitial gland, or so-called "interstitial tissue of Leidig," which is described as epithelioid cell accumulations imbedded in the sex glands of the male. These cell accumulations contain acidophilic and basophilic granules very similar to the cells of the suprarenal cortex, and like them are of mesodermal origin.[34] In women we understand by the term "interstitial gland" a cell complex developing from the atritic follicles of the theca interna.

It was formerly thought that the interstitial glands controlled the development of the primary and secondary sex characteristics and were therefore of great importance in determining general body conformation. Opposed to this view Meyer[35] states that

[31] Quart. Jour. Exp. Physiol., 1916, 214.
[32] W. Falta: Loc. cit., p. 176.
[33] J. J. R. Macleod: Loc. cit., 801.
[34] W. Falta: Loc. cit. p. 370.
[35] Zentralbt. f. Gynec., 1920, **16**, 593.

an interstitial gland in women does not exist, that there is no increase in these special cells in girls at puberty, that these cells are found in embryo at the sixth fetal month and these cells have nothing to do with sexuality, and, further, that the ovaries are not essential to the development of the secondary sex characteristics.

Conclusive evidence of the existence of a specific autocoid elaborated by the interstitial gland is so far wanting, it being probable that the influence of these glands on body growth and the sexual characteristics is very slight, since the great mass of reliable evidence assigns the control of the primary and secondary sexual characteristics to well-demonstrated influences from the other ductless glands.[36] [37]

Sex Glands to Pituitary, Thyroid and Adrenals. Physiologic relation of the ovary to the pituitary, thyroid and adrenals is demonstrated by abundant experimental and clinical evidence of an increased activity of the pituitary, the thyroid and the adrenals during pregnancy and by the marked changes in the sexual glands and alterations in their normal period of development in pathologic conditions affecting the pituitary, adrenal and thyroid glands (see above).

Thymus. While there is still active discussion as to whether the thymus should be included in the group of glands of internal secretion it seems reasonable in the light of the more recent literature to agree with Falta that, since it has been proven that the gland rapidly atrophies at puberty in both sexes, and since experimental removal of the ovaries in young animals is followed by rapid sexual development and a limitation of *somatic growth*, the theory of the presence of an internal secretion is tenable. Bucher[38] reports 8 cases in which thymectomy in children was followed by disturbance in growth and warns against thymectomy or roentgen-ray of the whole gland. The thymus, therefore, probably is closely related to the sex glands, upon which it influences a restraining action during the early years of life. This action is seen clinically in cases of thymic subinvolution, in which sex differentiation is incomplete and development of these organs arrested, while the skin is soft in texture, smooth and velvety with a fine covering of hair, while in the male there is little or no mustache or beard; the pubic hair likewise is sparse in both sexes, and in the male assumes the female characteristic distribution. The menses may be delayed or entirely lacking.[39]

Pineal. The function of the pineal gland is obscure. In cases in which its removal has been successfully accomplished (in the fowl) it has been found that body growth was stimulated and that

[36] Blair Bell: Loc. cit., p. 145.
[37] Blair Bell: Abstract Endocrin, 1921, **5**, 660.
[38] Schweizer Arch. f. Neurol. u. Psych., Zurich, 1921, **8**, 208–215.
[39] W. Timme: Neur. Bull., 1921, **3**, 1–3, and Address before Philadelphia Pediatric Society, December 3, 1921, author's notes.

the sexual characteristics developed more quickly.[40] This study would seem to indicate that when new growths affecting the pineal gland are accompanied by precocious sexual development, due to hypofunction of this organ, and that therefore this gland maintains in some obscure way an inhibitory influence upon the development of the sexual organs. On the other hand, Sisson and Finney,[41] in a series of carefully conducted and controlled experiments on rats, failed to find that feeding pineal powder in large doses in any way influenced the growth, nutrition or sexual characteristics or sexual development of the test animals.

No histologic or experimental evidence has yet been produced to demonstrate an internal glandular function of the pineal body.

Pancreas. The many experimental studies that have been performed in an effort to demonstrate the presence of a specific internal secretion of the pancreas have so far been unsuccessful. No secretion has yet been isolated or defined chemically; neither are we certain as to the path through which, if such be present, it is given off. Owing to the extreme vascularity of the pancreas it has been suggested that a substance may be given off bound to the blood corpuscles. Those who have argued for an internal secretion from this gland assign to the islands of Langerhans this suppositious role, because experimental evidence makes the functional independence of the insular apparatus highly probable.[42]

Spleen. The discussion would not be complete without reference to recent literature bearing on the probable existence of an internal secretion elaborated by the spleen. Nathan B. Eddy[43] reviews the literature to date and appends a bibliography of forty-nine references. After a careful discussion of all pertinent data Eddy concludes that the hypothesis that the spleen produces an internal secretion is supported by (*a*) the changes noted in the erythrocytes after splenectomy; (*b*) the modification of the blood picture in hyperplasia of the spleen ameliorated in some cases by splenectomy, and (*c*) the specific effects on the red blood corpuscles produced by the injection of splenic extract.

The result of this study has been rather discouraging, because of the persistent recurrence of contradictory results in the experimental work done by equally competent observers, which forces the conclusion that despite the great amount of work done, the undoubted accuracy of the evidence presented and the apparent reliability of the deductions based upon them we actually know but a small fraction of what is yet to be learned of the functions and correlations of this interesting group. The opinion is further strengthened by the fact that in much of the clinical evidence there is often no firmer foundation than the enthusiasm of the self-styled endocrinologist.

[40] J. J. R. Macleod: Loc. cit., p. 820.
[41] Jour. Exper. Med., 1920, **31**, 335.
[42] W. Falta: Loc. cit.
[43] Endocrin, 1921, **5**, 461.

AURICULAR FLUTTER, WITH REPORT OF CASES.

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The term "auricular flutter" was first applied by McWilliams in 1887, and the designation has been retained up to the present time. Since the advent of the electrocardiograph the condition has been recognized with far greater frequency.

The first experiments reported from the laboratory were published by McWilliams.[1] He first observed the rapid response to faradization on the auricles of a dog and a cat, and, as he says, "the application of faradic current sets the auricle into a rapid flutter, no distinct signs of incoördination (being) present." The foregoing experiments of McWilliams differed, therefore, from experiments on voluntary muscle in that faradization of voluntary muscle produces tetanus, whereas faradization of cardiac muscle produces a series of rapid, coördinated contractions. This difference is due in part to the fact that in the heart muscle a comparatively long inhibitory period follows upon each ventricular contraction, during which the heart is not able to respond to any stimulus, while a second factor is found in the sphincter-like arrangement of the muscle fibers around the openings of the superior and inferior venæ cavæ. The length of the inhibitory period peculiar to each auricle will naturally influence the speed of its flutter. Consequently, some auricles will flutter at the rate of 200 per minute, others at 300. According to Lewis,[2] the highest ever observed in man was 335. One of our cases, as the record shows (Fig. 11), attained a speed of 360 per minute, and at times the rate increased to 375.

Clinically the term auricular flutter was first applied by Jolly and Ritchie,[3] in 1905, in the report of their case of auricular flutter associated with complete heart-block.

REPORT OF CASES

Case I.—E. H., aged fifty-six years, laundry worker, entered the hospital November 8, 1916, and was discharged one month later (December 8) improved. On admission she was complain-

[1] Jour. Phys., 1887.
[2] Lancet, 1912, **2**, 1418.
[3] Heart, 1910–11, **2**, 177.

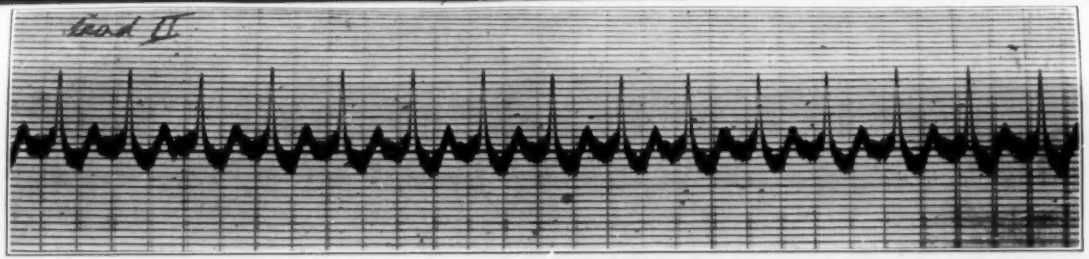

FIG. 1 (Case I).—Electrocardiogram on admission November 8, 1916, showing auricular flutter. Auricular rate 300. Ventricular 150. Time in fifths of a second.

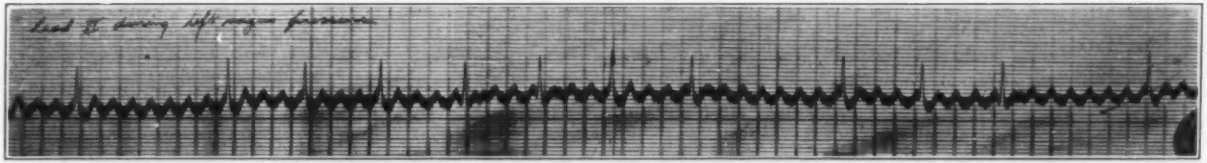

FIG. 2 (Case I).—Curve of the same patient, showing effect of left vagus pressure. Auricle uninfluenced. Ventricle slowed from 3:1 to 8:1. Time in fifths of a second.

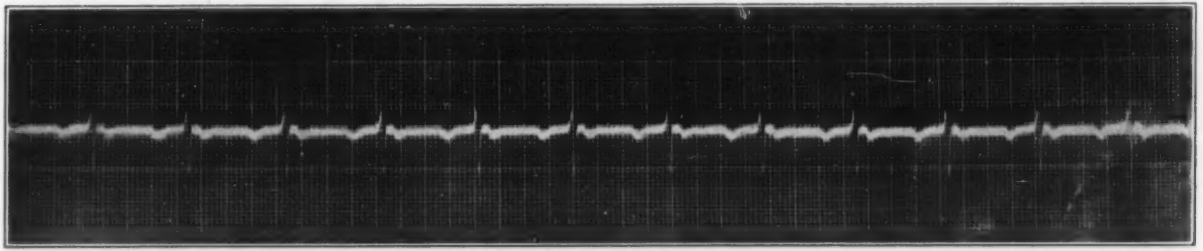

FIG. 3 (Case I).—Electrocardiogram taken in June, 1921, showing normal rhythm. Time in twenty-fifths of a second.

ing of dyspnea, cough, swelling (of feet, legs and abdomen), continuing for three weeks, with gradual onset. In her past life she had had rheumatic fever in 1914 and reported no other infectious diseases. Her family history was negative. The essential physical findings, upon the examination, were as follows: Orthopnea, many carious teeth, marked pyorrhea. Lung bed showed fluid at the right base. Examination of heart: The apex was in the fifth space, 14 cm. from the median line; rate regular, 148 per minute; no murmurs or accentuations audible. Blood-pressure: systolic, 180; diastolic, 100. Laboratory findings were negative except for a trace of albumin in her urine. Wassermann was negative. Electrocardiogram taken on admission showed auricular flutter; auricular rate, 300; ventricular, 150 (Fig. 1). The patient was put on large doses of digitalis. In two weeks her pulse-rate came down to 60, when digitalis was discontinued. An electrocardiogram taken on December 2, when the patient was up and about, showed an auricular rate of 300, with the ventricle responding to every fourth auricular beat. Pressure applied to the left vagus caused the ventricle to respond to every eighth auricular beat and had no influence whatever on the fluttering auricle (Fig. 2). An electrocardiogram taken recently showed a normal rhythm (Fig. 3).

Case II.—C. D., age sixty-two years, shipping clerk, was admitted to the hospital April 7, 1920, and discharged May 3, same year, improved. On admission he complained of dyspnea, cough and palpitation for the four weeks preceding. His past history was negative except for mutiple alveolar abscesses, causing him to have all teeth removed. The family history was negative. Physical examination showed a poorly nourished male, presenting cyanosis and dyspnea. The lungs showed many rales at both bases. Heart: The apex in fifth interspace, 11 cm. from median line; palpation of precordium was negative; the sounds were of poor muscular quality, suggesting fetal heart sounds; rate regular, 90 per minute. Blood-pressure, 110/75. Laboratory findings were negative. Wassermann reaction negative. The electrocardiogram taken on admission showed auricular flutter; auricular rate, 300 ventricular, 90 (Fig. 4). The patient received large doses of digitalis during his stay in the hospital. His auricular rate did not vary, but the ventricle, responding to the digitalis, slowed down to as low as 60. At this time the patient was discharged improved, and referred to the Cardiac Clinic, where he continued to receive digitalis in large doses. On May 11, because of a large pulse deficit being noted, an electrocardiogram was taken which showed auricular fibrillation (Fig. 5). On May 17 he became normal in rhythm and has remained so to the present time (Fig. 6).

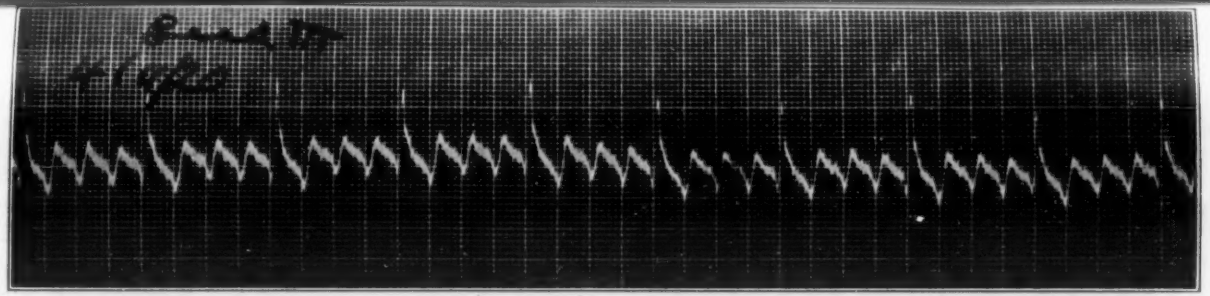

FIG. 4 (Case II).—Electrocardiogram taken April 4, 1920, showing flutter. Auricular rate 300. Ventricular 90. Time in twenty-fifths of a second.

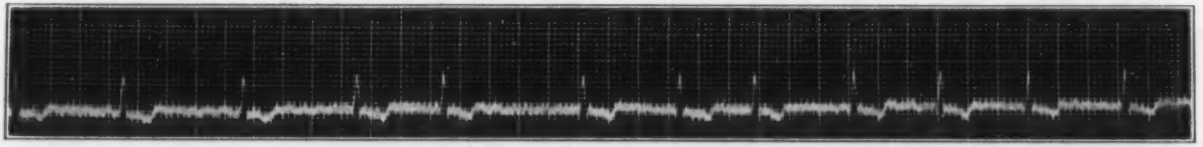

FIG. 5 (Case II).—Curve of the same patient taken May 11, 1920, showing auricular fibrillation following administration of large doses of digitalis. Time in twenty-fifths of a second.

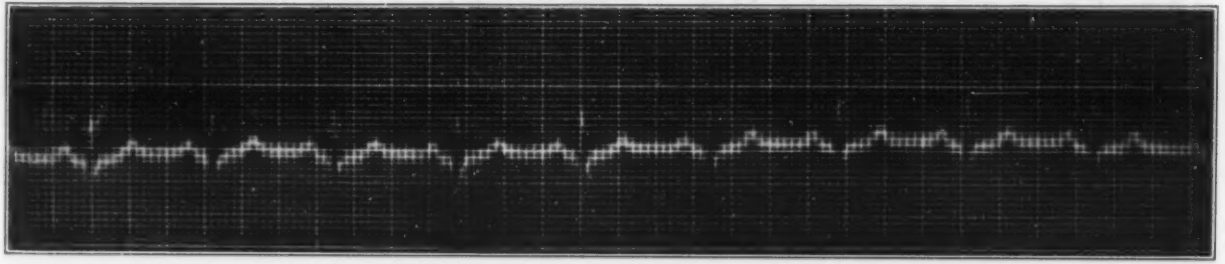

FIG. 6 (Case II).—Electrocardiogram taken May 17, 1921, showing normal rhythm. Time in twenty-fifths of a second.

CASE III.—A. K., aged fifty-eight years, dressmaker, was first admitted to the hospital in July, 1919, and discharged in September, 1919. On admission she complained of dyspnea, precordial pain, cough and attacks of syncope beginning three months prior to admission, the symptoms coming on gradually. In the past she had had measles, scarlet fever, rheumatism as a child, and influenza-pneumonia eight months prior to admission. Family history was negative. Essential physical findings at time of admission showed an elderly woman presenting poor muscular and bony development. The patient was orthopneic. Oral hygiene was markedly neglected and the teeth showed many cavities. The lung presented many moist rales at both bases. The heart: Apex in sixth space, 15 cm. from median line; rate, 90—regular; sounds of poor quality; no murmurs or accentuations audible. Liver 7 cm. below costal margin. Edema of both legs. Blood-pressure, 130/90. Urine examination was negative. Phthalein, 71 per cent at end of two hours. Wassermann reaction negative. Electrocardiogram taken on day of admission showed flutter; auricular rate, 270; ventricular, 90 (Fig. 7). The patient was put on large doses of digitalis, which caused the ventricular rate to fall as low as 44, but producing no effect whatever on the auricular rate. She was discharged, improved, on September 9; her auricle was still fluttering, but the ventricle had slowed down to about 70. The patient was readmitted October 21, 1919, with similar symptoms as when first entering the hospital, and died December 22, 1919. Electrocardiograms to the number of fifteen were taken, and all showed auricular flutter, despite the fact that she was being given huge doses of digitalis. Pressure upon the left vagus caused the ventricle to slow down but had no effect upon the auricle. Figs. 8 and 9 demonstrate the effect of pressure on the left vagus in this case, the auricle beating 14 times to 1 ventricular contraction in Fig. 8 and 22 times to 1 in Fig. 9.

CASE IV.—L. B., aged thirty-eight years, nurse by occupation, entered the hospital complaining of dyspnea, palpitation, feeling of oppression over the precordium and a sense of suffocation for three days prior to admission. She was admitted on December 15, 1920, and discharged March 6, 1921. Her family history was negative. In her past life she had had many severe infections up to the age of twelve, but since then had never been ill until admission. On physical examination she showed good muscular development and nutrition, with moderate amount of dyspnea. Teeth were in good condition. Tonsils small. Heart: Apex in fifth interspace, 8 cm. from median line; heart sounds of poor muscular quality; rate 90, regular; no murmurs audible. Blood-pressure, 130/80. Wassermann reaction negative. All laboratory tests, including those for hyperthyroidism, were negative.

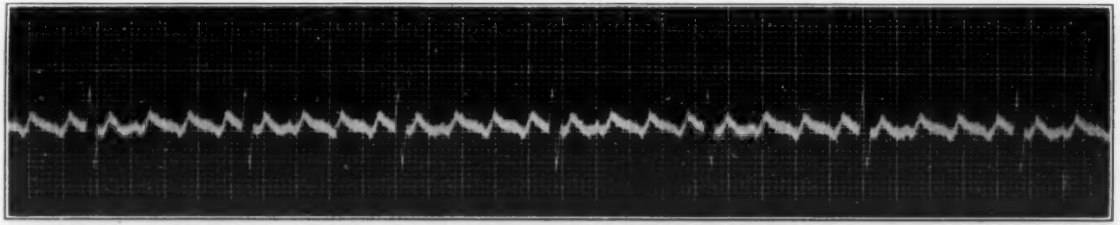

FIG. 7 (Case III).—Electrocardiogram taken on admission July, 1919, shows auricular flutter A = 270. V = 90. Time in twenty-fifths of a second.

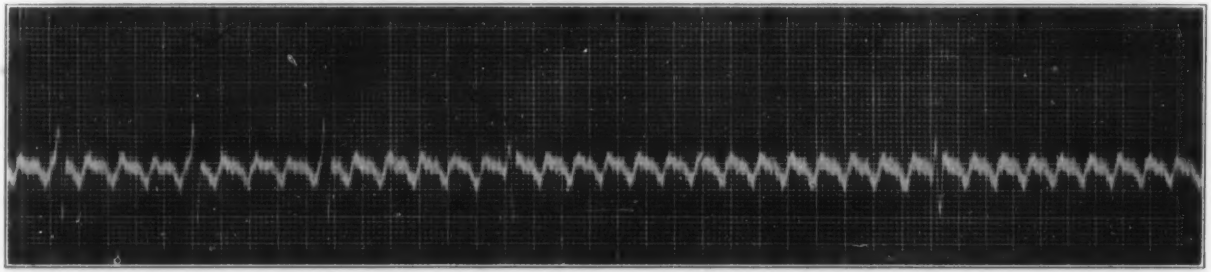

FIG. 8 (Case III).—Curve of the same patient showing the effect of left vagus pressure. Ventricle slowed down from 1 : 4 to 1 : 14. Time in twenty-fifths of a second.

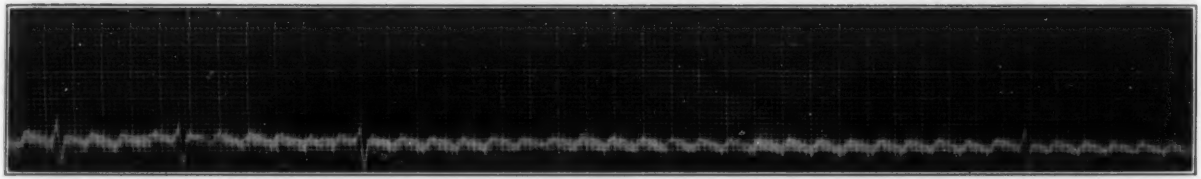

FIG. 9 (Case III).—Curve of the same patient showing the effect of left vagus pressure. Ventricle slowed down from 1:3 to 1:22. Time in twenty-fifths of a second.

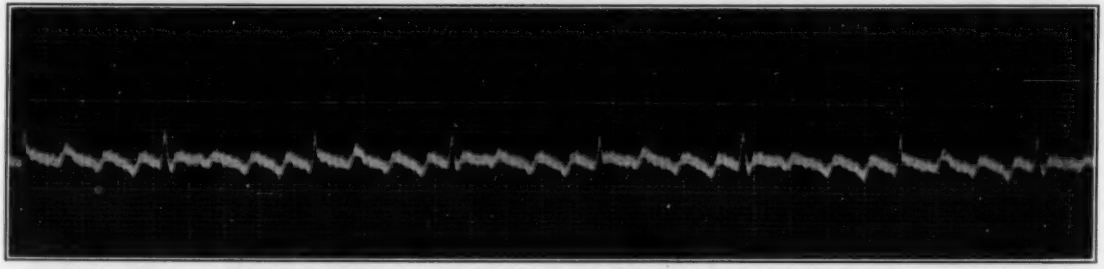

FIG. 10 (Case IV).—Electrocardiogram taken on admission December, 1920, shows flutter. This patient shows flutter up to the present time. Rate A = 300. V = 90. Time in twenty-fifths of a second.

Electrocardiogram showed auricular flutter; auricular rate, 300; ventricular, 90 (Fig. 10). The patient was put through an intensive course of digitalis therapy for thirty days, with a view to causing the heart to fibrillate, or, if this were not possible, of causing the ventricle to diminish its speed. The digitalis had no effect on the fluttering auricle, as was shown by the electrocardiograms taken at frequent intervals, but caused a slowing of the ventricle. When the ventricular rate fell below 60 digitalis was discontinued, in anticipation of auricular fibrillation. Unfortunately this did not take place, and the patient was put on atropine for a period of fourteen days, during which time the ventricular rate rose to 80, the auricular remaining the same. Exercise, emotion, even change of posture at times, caused an increase of the ventricular rate, but the fluttering auricle was uninfluenced throughout her entire stay in the hospital.

An electrocardiogram taken August 3, 1921, shows auricular flutter; auricular rate, 300; ventricular, 88. The patient is up and about and feels little discomfort.

Case V.—St. H., aged fifty years, milliner by occupation, was admitted to the hospital January 27, 1921, complaining of sudden attacks of collapse with momentary unconsciousness during the last four years, with gradual onset. Dyspnea for the same period. Her family and past history, as far as could be ascertained, were negative. Physical examination showed the following essential points. The patient was a poorly developed, poorly nourished woman, presenting a moderate amount of dyspnea; teeth were noted to be in poor condition. Heart: Apex impulse in fifth interspace, 9 cm. from median line; rate 140, regular; no murmurs or accentuations audible; second aortic sound equals second pulmonic; peripheral arteries showed a moderate sclerosis. Laboratory findings were entirely negative. Electrocardiogram taken on admission showed a simple tachycardia. After a week's stay in the hospital the tachycardia changed to auricular flutter, with complete heart-block (Fig. 11). All electrocardiograms excepting two have shown auricular flutter; auricular rate, 360; ventricular rate, 30, and complete heart-block. At one time the patient showed complete heart-block with normal auricular rate: A rate is 90, V rate is 30 (Fig. 12). In this case the auricular sounds were distinctly audible when the auricles were fluttering, as described more fully under *Physical Signs*, below.

Electrocardiograms taken recently (Figs. 12a, 12b, 12c) show an impure flutter, with a transition to fibrillation in all three leads and numerous ventricular extrasystoles. These electrocardiograms demonstrate clearly the close association between auricular flutter and auricular fibrillation. The immediate passage of one into the other is clearly shown.

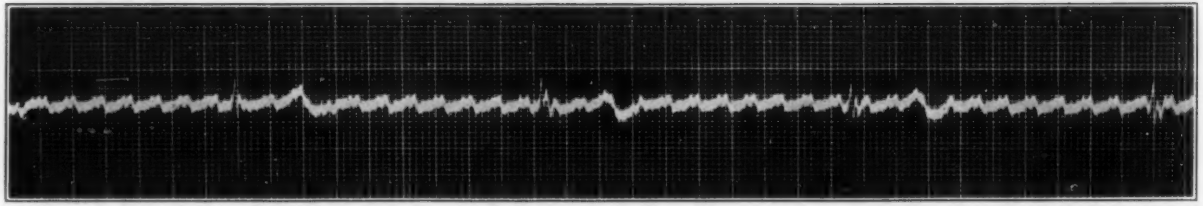

FIG. 11 (Case V).—Electrocardiogram showing auricular flutter (auricular rate 360) with complete heart-block. Ventricular rate 30. Auricular rate unusually high. Time in twenty-fifths of a second.

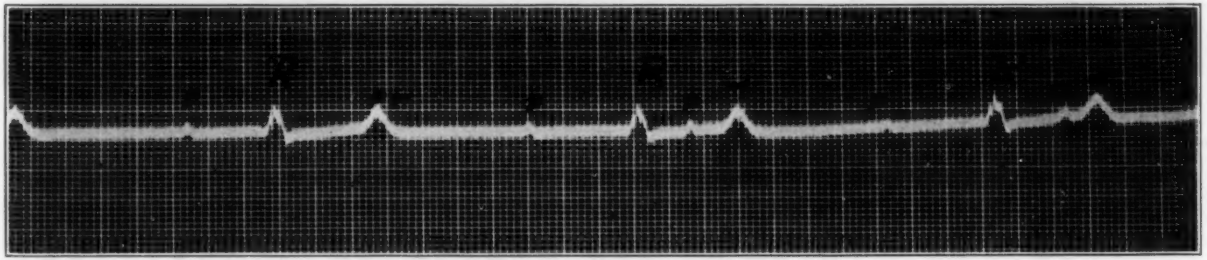

FIG. 12 (Case V).—Curve of the same patient showing complete heart-block. Auricular rate normal. Ventricle beating at its own intrinsic rate of 30. Time in twenty-fifths of a second.

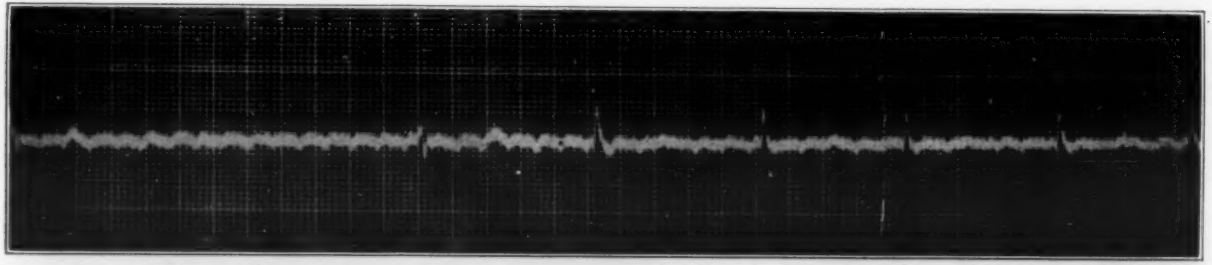

FIG. 12 *A* (Case V).—Lead I Electrocardiogram taken recently showing impure flutter with transition to fibrillation and many premature ventricular beats.

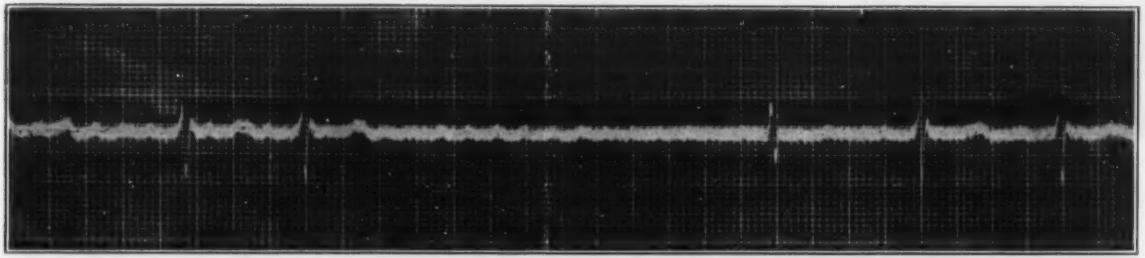

FIG. 12 *B* (Case V).—Lead II showing the same conditions as Lead I.

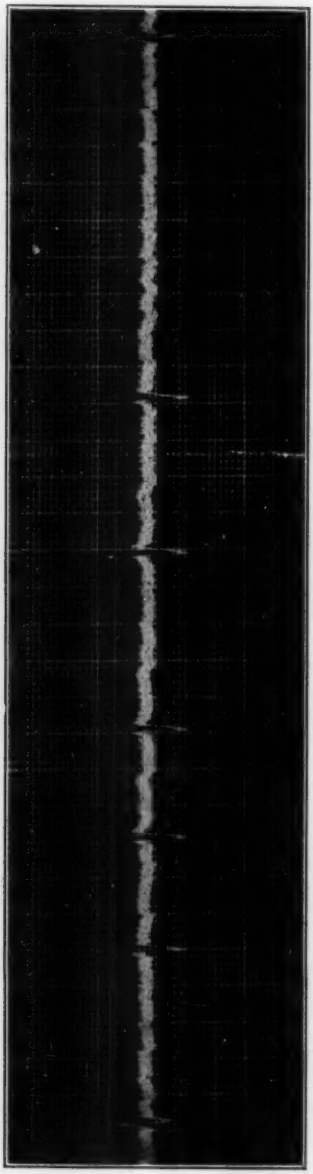

FIG. 12 *C* (Case V).—Lead III showing the same changes as Leads I and II.

CASE VI.—McK., aged thirty-three years, houseworker by occupation, was admitted to the hospital December 4, 1919, complaining of dyspnea, palpitation, sweating and enlargement of

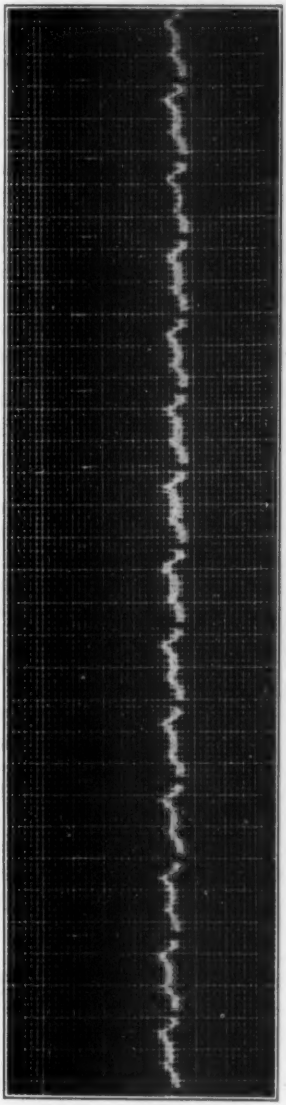

FIG. 13 (Case VI).—Curve taken December, 1919, showing simple tachycardia.

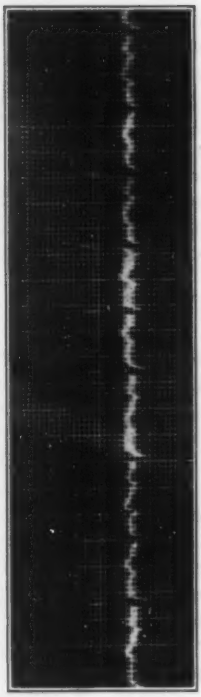

FIG. 14 (Case VI).—Same case showing auricular flutter. A = 270. V = 120. Time in twenty-fifths of a second.

her neck for five months prior to admission. Her family and personal history were entirely negative. On physical examination she showed moderate exopthalmos, fine tremor and moist skin. Tonsils were found to be hypertrophied and inflamed. There was a symmetrical bilateral enlargement of the thyroid gland, with bruit. Heart: Apex in fifth interspace, 9½ cm. from median line; rate, 130, regular; no murmurs audible. Blood-pressure, 128/85. Laboratory findings: The blood picture showed the mononucleosis of hyperthyroidism; Wassermann reaction negative, the remaining laboratory tests confirmed the diagnosis of hyperthyroidism. The patient had three applications of radium, on December 7, 13 and 26 respectively. Dose, 120 mg.; exposure four hours. Electrocardiographic study of this patient was very interesting, inasmuch as it demonstrated the rapid pas age of one arrhythmia into another. The electrocardiograms showed the following transitions in the order named: Simple tachycardia rate 120 (Fig. 13); partial block; auricular fibrillation; normal rhythm; auricular flutter: A rate is 270; V rate is 120 (Fig. 14); and auricular fibrillation. On January 21, 1920, the patient developed pneumonia and died eight days later. Necropsy showed acute pericarditis and endocarditis, with lobar consolidation of both lower lobes of the lungs.

Case VII.—M. R., aged forty-two years, housewife, entered the hospital December 2, 1919; complained of dyspnea, palpitation, nervousness, weakness, precordial pain, frequent nose-bleeds, all during the three months prior to admission. Her family history was negative. In the past she had some of the childhood diseases but no other infections. In 1909, or ten years prior to admission, she had experienced symptoms similar to the present ones, and in 1910 partial thyroidectomy had been performed, since which time she had been entirely well, until about five months prior to admission. On physical examination moderate exopthalmos, enlargement of the right lobe of the thyroid gland and fine tremor were found present. Heart: Apex in fifth interspace, 10 cm. from median line, sounds rapid, regular, rate 120; blowing, systolic murmur at base and apex, second aortic sound accentuated; no shocks or thrills. Laboratory findings confirmed the diagnosis of hyperthyroidism. Wassermann reaction was negative. The patient had five exposures of radium of four hours' duration each. Dose, 120 mg. Electrocardiographic study showed the patient going through the stages of tachycardia, of hyperthyroidism, auricular flutter, auricular fibrillation. Rate of flutter, A rate is 300, V rate is 120. This was demonstrated on one occasion only.

Case VIII.—S. C., aged sixty-six years, governess, entered the hospital May 6, 1921, complaining of dyspnea and palpitation

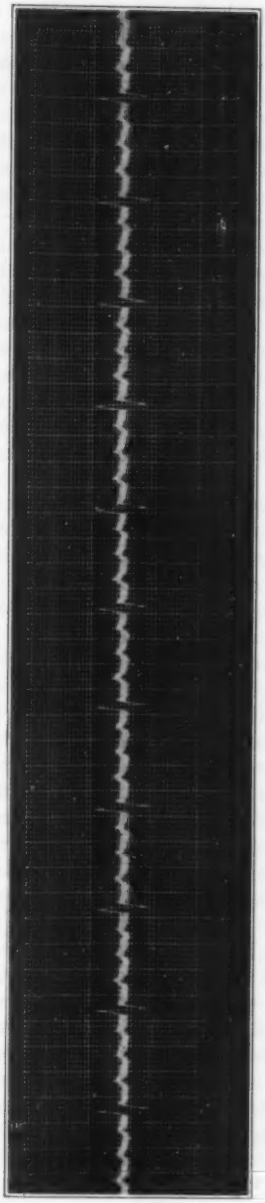

FIG. 15 (Case VIII).—Curve taken June, 1921, showing auricular flutter. A = 300. V = 90. Time in twenty-fifths of a second.

on exertion for one and a half years past. Had been taking tincture of digitalis for six months prior to admission, without improvement. During her past life she had suffered from frequent attacks of tonsillitis. Physical examination showed an obese woman, orthopneic; tonsils and teeth were negative. Heart: Apex in fifth interspace, 10 cm. from median line; rate 144, regular; no murmurs, shocks or thrills. Blood-pressure 185/125. Laboratory tests: Blood-picture of secondary anemia; Wassermann negative; urine, faint trace of albumin, with many granular casts; Phthalein 16 per cent at end of two hours; urea nitrogen in blood 26.4 mg.; blood sugar, 222 mg. The patient is still in the hospital. The first electrocardiogram showed an impure flutter. One week later this changed to a typical flutter, with an auricular rate of 300 and a ventricular rate of 90 (Fig. 15). Digitalis had no effect and quinidine sulphate has been tried without effect.

Definition. Auricular flutter is a condition characterized by rapid, regular and coördinated action of the auricles, in which the latter attain a speed so great that the ventricles are unable, or rarely able, to respond to each auricular impulse and thence a partial, or at times a complete block, is set up. The impulses no longer arise from the sinoauricular node, but from some other portion of the auricle.

As to what is the method of stimulation which in man leads to flutter and its coördinated states, this is as yet undetermined.

Pathology. Pathology of these cases is variable, as can be noted from the case reports presented above. Usually one of the following conditions is found to be present: old-standing disease of the vascular system or of the cardiac muscle; acute or chronic inflammation of the endocardium or of the myocardium, usually of infectious origin, such as lues, rheumatic fever, influenza and the like; infections of the pericardium and disease of the conducting system of the heart (also usually of infectious origin) coexistent with and spreading from endocardial or pericardial infection. Cases I and III in our series followed attacks of acute rheumatic fever, with definite cardiac involvement. Cases VI and VII gave a history of hyperthyroidism and were suffering with that condition on admission. Case V was definitely arteriosclerotic, with no history of infection. Case VIII was a cardionephritic, with history of frequent tonsillitis. Case II had a definite myocarditis on admission with no other history of infections than multiple alveolar abscesses. Case IV had no history of infection in the immediate past but had had many severe infectious diseases when a child.

Symptoms. The symptoms of auricular flutter are those of cardiac insufficiency of varying degree. The cardinal symptom, is that of dyspnea, all of our histories showing it to be the chief complaint. The shortness of breath is usually accompanied by

a sense of oppression and a feeling of suffocation and impending death. Most of the patients are conscious of palpitation of the heart, more especially so, those in whom the ventricle responds to every second beat. In some cases, particularly those in which a carditis has previously existed, owing to the gradual development of myocardial insufficiency, the output of the heart decreases and causes an impairment of cerebral circulation; a common complaint, therefore, is dizziness and faintness, especially so where there is a complete heart-block. Case V complained on admission of sudden attacks of collapse with momentary attacks of unconsciousness during a period of four years, a picture fairly typical of Stokes-Adams syndrome. The same symptoms were the principal ones also in Cases II, IV and V, in which no other pathology was noted clinically.

When other organic lesions are found the symptomatology is more complicated and must be correspondingly modified or enlarged.

Physical Signs. There may be none whatever; when the amount of cardiac insufficiency is slight (Case IV) and when the rate of the flutter may be 1 to 4 with a radial pulse of 80, none are likely to be noted. It then becomes impossible to make the diagnosis clinically. Most of the patients, however, present signs of endo- or myocardial insufficiency. In Case V of our series an additional interesting physical sign was noted on auscultation. This case, as stated in our case report, had at times auricular flutter with complete heart-block, the rate of the auricle being 360 and of the ventricle 30, which was its own intrinsic rate. On auscultation a very rapid tick-tack sound, resembling that of a fetal heart, was audible over the entire precordial area; it was heard best just inside the apex impulse. At the same time there could be heard the loud, muscular sound produced by the ventricular contraction, which occurred infrequently, approximately thirty times per minute. The auricular sounds in this Case V were very definite and were demonstrated to the students on several occasions. An interesting picture of flutter was shown by Hertz and Goodhart,[4] in 1908 upon the fluorescent screen, the auricular movements being distinctly visible.

Diagnosis. As may be readily appreciated, diagnosis of auricular flutter clinically, because of the few definite symptoms and physical signs pertaining to this condition alone, is exceedingly difficult. Before the introduction of the electrocardiogram the diagnosis was principally made on the jugular pulsation and the pulse-rate. The rapid pulsation of the jugular veins was diagnosed usually by visual observation, and occasionally by means of a polygraph tracing of the jugular pulsations and radial pulse. But, as generally admitted, jugular pulsations are of very questionable value,

[4] Quarterly Jour. Med., 1908–09, **2**, 213.

especially in obese patients. The human eye is not trained to perceive the rapid vibration of the great veins at the base of the neck, particularly when the rate is between 200 and 300 per minute; consequently the diagnosis of auricular flutter was but very infrequently made. However, since the advent of the electrocardiograph the condition of auricular flutter has been found a very much more common one than at first supposed. It has frequently been stated, and often erroneously taught in our medical schools, that the diagnosis of auricular flutter should not be made unless the ventricular rate reaches at least 150. As a matter of fact the first case reported on the subject in the literature was of a man, aged sixty-one years, with an auricular rate of 273 and a ventricular rate of 34. This man was under observation for many years and showed this condition almost constantly; he suffered from frequent attacks of Stokes-Adams syndrome. In our own series a ventricular rate of over 100 was rare indeed, and notably in one case (V) which closely resembles Jolly and Ritchie's case,[5] the ventricular rate has been for long periods of time between 30 and 40. Of course, if the ventricle responded to every contraction, as in a case reported by McKenzie,[6] we would have a high ventricular rate; in that case the response of the ventricle was 280 to 300. However, this condition is extremely rare, and unless substantiated by electrocardiographic evidence it would incline us rather to consider it a case of paroxysmal tachycardia.

Etiology. As regards the etiology, Lewis[7] has recently advanced Mine's ingenious hypothesis to explain the origin and mode of propagation of the impulses producing flutter of the auricles. According to him, the rapid auricular contractions of flutter depend on an excitation wave in the auricle which travels continuously in a circular fashion around the openings of the great veins and spreads centrifugally with each flutter contraction throughout the entire portion of the auricle. To this fundamental condition he has applied the term "circus movement."

It will be of value to discuss, at this time, the relationships between paroxysmal tachycardia, auricular flutter, and auricular fibrillation, which are all closely allied and probably parts of the same pathological condition, as indicated by the frequency of the immediate transition of one into the other. A normal auricular contraction is initiated at the sinoauricular node and spreads in a definite direction throughout the entire auricular tissue. An abnormal impulse, causing a contraction of the auricle, originates in some region of the musculature other than the pace-maker, as demonstrated by an abnormal auricular complex in an electrocardiogram. Occasionally, small groups of premature auricular contractions may come close upon one another, giving rise to short parox-

[5] Loc. cit.
[6] Heart, 1910–11, **2**, 317.
[7] Heart, 1920, **7**, 293.

ysms of tachycardia. Usually they are ushered in by a shortened diastole and end with a compensatory pause.[8] Paroxysmal tachycardia and auricular flutter have ectopic pace-makers in the auricles, outside of the sinoauricular node; they are generally characterized by the same shortened diastole and compensatory pause, and are graphically shown when one is fortunate enough to get a record at the particular moment of the beginning of a flutter or paroxysm. The similarity of single or of groups of premature contractions, paroxysmal tachycardia, auricular flutter and auricular fibrillation can be shown further by the fact that the ectopic focus produces a complex different from the normal auricular P wave in the electrocardiogram. When the impulses again become initiated in the normal pace-maker the auricular complex becomes once more normal. It is an established fact, as pointed out by Lewis[9] and many other observers, that auricular flutter and fibrillation are closely allied.

In a theoretic generalization based upon our clinical report it seems to us that we would be justified in the assumption of an even closer relationship between the three conditions than has thus far been claimed in the literature. In auricular flutter there is but a single point of origin whence the excitation wave takes its course on its circus movement throughout the auricle; when flutter is established, the wave of excitation becomes independent of its point of origin. In auricular flutter the excitation wave consumed always the same period of time over the same stretches of auricular tissue.

It is our belief that the excitation wave follows the circus movement throughout the auricles in all three conditions. This wave of excitation travels regularly, covering the same distance in the same period of time, both in paroxysmal tachycardia and in pure flutter. In impure flutter and fibrillation the regularity of the excitation wave is interrupted in its passage through the auricular tissue, this interruption being more marked in fibrillation. In impure flutter the rhythm varies but slightly.

Our views are substantiated by experimental clinical work, which bears out the work of Lewis.[10] He believes that impure flutter differs from pure flutter in that there exists, in the former, an established local obstruction or actual barrier (block) which deflects the waves along new sinuous paths. In fibrillation the same condition of local barrier is present, only the barriers are multiple and involve most of the auricle. Whether the hypothesis of a single circular wave following a sinuous curve throughout the auricle holds true in auricular fibrillation, or whether there are multiple waves following circular paths through the auricle, we must con-

[8] Lewis, T.: Clinical Electrocardiography, p. 60 (Fig. 54).
[9] Lancet, Loc. cit.
[10] Heart, 1920 **7**, 127, 293.

fess ourselves, from our clinical observations, as still in doubt. There seems, however, no valid reason why there should not be, in auricular fibrillation, multiple points of origin with the excitation wave in the fibrillating auricle still following the circus movement; neither does there seem any reasonable objection to the hypothesis that two waves of excitation can travel in a circular fashion throughout the auricles, and we think that Lewis's theory fully explains the mode of propagation of impulses in the fibrillating auricle.

As a result of our observations we are inclined to the belief that auricular fibrillation and paroxysmal tachycardia are but forms of auricular flutter. It is known that in fibrillation the auricular rate is about 470 per minute, the ventricle responding irregularly, in no definite relation and ratio to the auricular movement; this results in a partial or impure block, almost identical with impure flutter. Drury and Iliescu,[11] by means of chest-leads, were able to eliminate the muscular interference and to obtain leads from the sagittal plane of the body. These chest-leads, taken as an ordinary lead 2 from a case of auricular fibrillation, showed coarse oscillations, about 470 per minute. The ordinary lead 2, taken at the same time, showed the usual type of irregular oscillations of the auricle obtained from limb leads. The limb leads seem to be unfavorable in demonstrating fibrillation, as it actually exists, in close relationship to flutter and paroxysmal tachycardia.

As taught up to the present time, auricular flutter, paroxysmal tachycardia and auricular fibrillation have been considered as separate and distinct from one another. In our opinion, they are one and the same condition, characterized merely by three different stages of varying degree and intensification. Theoretically it may be said that paroxysmal tachycardia is the first stage, flutter the second and fibrillation the third. We believe that all three manifestations can be fully explained by the theory of circus movement. As is frequently said, Nature never draws lines, and by means of the transitions which daily are presented in given cases by the electrocardiograph we are beginning to appreciate the closeness of the three conditions. The transition between auricular flutter and auricular fibrillation in the form of impure flutter is very well illustrated in our Case V.

In paroxysmal tachycardia the ventricle responds to every auricular impulse. Cases of auricular flutter, however, in which the ventricle responds to each impulse of the auricle are extremely rare; and for the simple reason, as we believe, that the ventricle cannot respond to every auricular impulse at so high a rate of speed for any length of time. Paroxysmal tachycardia, being of comparatively short duration, admits of the possibility of the ventricle maintaining an even gait with the auricle.

[11] Heart, 1921, 8, 171.

We consider the block in auricular flutter and auricular fibrillation as a protective measure on the part of Nature in order to maintain the cardiac tone at par as long as possible, and for the simple reason that in a great many cases the disturbance in rhythm appears to be purely functional. It is in the study of the transition from one condition to the other that the intimate relationship between the three becomes apparent. This extended and unbroken study was obviously impossible prior to the introduction of the electrocardiograph. In our series of cases 5 out of the 8 showed fibrillation at one time or another.

Cases of flutter experiments,[12] conducted to determine the effect of vagal stimulation, have led to the observation that large doses of atropin, although causing acceleration of the ventricle, through vagus nerve palsy, have no effect on the auricular rate. This observation has been corroborated by the clinical facts brought out in the study of our series of 8 cases. Pressure on the vagus, as shown in Cases I and III (Figs. 2, 8 and 9) produces a marked slowing of the ventricle but does not influence the auricular rate. In Case III pressure on the left vagus altered the response of the ventricle from 3 to 1, to 21 to 1 (Fig. 9). Exercise, emotion and change of posture caused acceleration of the ventricle, but had a very slight effect, if any, on the fluttering auricle. Evidently the normal inhibitory action of the vagus, although still acting on the ventricle, did not influence the auricle.

Whether the etiology of auricular flutter lies in the lack of inhibition of the vagus on the auricle, stimulation of the sympathetic or accelerator being purely nervous, or whether the cause is in a pathologic change in the musculature of the auricle itself, is not definitely proven. Possibly both causes may contribute.

In all cases so far reported the age incidence does not seem to play any particular role. Cases have varied in ages from twenty-one to seventy-two; in our series the youngest was thirty-three and the oldest sixty-six. While auricular flutter may occur at almost any age the greatest number of cases represent middle life.

Prognosis. The prognosis of auricular flutter, as far as our series of cases can be said to lead to any conclusion, is problematical. It may be said, however, that the outlook in our series was modified by the complications which went along with each case. Case III died of kidney disease, Case VIII of pneumonia. In pure auricular flutter without any other complications the prognosis seems to be more favorable. The rhythm may return to normal, as in our Cases I and II (Figs. 3 and 6), or the heart may continue to flutter for years without any serious symptoms or discomfort to the patient. In the presence of other complications the lowered efficiency of the heart muscle in flutter, due to the very rapid con-

[12] Hertz and Goodhart: Quarterly Jour. Med., 1908–09, **2**, 213.

traction over a long period of time with an extremely shortened diastole, has a serious aspect. Cases of auricular flutter with complete heart-block, accompanied by syncopal attacks, present an uncertain future.

Treatment. When the case first comes under observation the patient should be put at rest in bed until his cardiac reserve has been increased. Digitalis is a drug of great value in this condition. Large doses, preferably in the tablet form, or intravenously, should be administered, with a view to causing the auricle to fibrillate. If this is accomplished the digitalis should be discontinued. Usually the auricle will then become normal. Unfortunately in some cases digitalis does not produce any effect on the heart other than slowing the ventricle, even when huge doses are administered. When digitalis fails to produce the desired effect the patient should lead a sedentary and uneventful life, to maintain the cardiac reserve at par. In all cases where possible electrocardiograms should be taken at stated intervals in order to judge the effect of the digitalis.

From the results obtained by us with quinidin sulphate we cannot at present draw any definite conclusions, as we used it in a few cases only.

Summary. 1. Auricular flutter is a condition characterized by rapid, regular and coördinated action of the auricle, in which the latter attains a speed so great that the ventricle is unable, or rarely is able, to respond to each auricular impulse, and thus a partial or a complete block is set up.

2. The symptoms depend upon the amount of the cardiac insufficiency and the presence or absence of complications, which will modify them. Dyspnea accompanied by palpitation and precordial distress are the predominant symptoms. In the presence of complications the symptoms will depend on the pathology.

3. The diagnosis of auricular flutter can in some cases be made with a sphygmograph tracing of the large veins and the radial pulse; but it is frequently unsatisfactory and sometimes impossible. Observation and auscultation of the patient is of little use in diagnosis of this condition. It can be definitely established only by the use of the electrocardiograph.

4. Our clinical experience bears out the experimental work. We believe that paroxysmal tachycardia, flutter and fibrillation are stages of the same pathologic condition causing cardiac insufficiency. We deem paroxysmal tachycardia to be the first stage, flutter the second and fibrillation the third.

5. Eight cases in all are here reported. In comparing them the most essential findings can be summarized as follows: In all our cases the auricle showed a remarkable stability while fluttering. Atropin, rest, exercise or emotion, while affecting the ventricle, had no effect whatever on the auricular rate. Five

of the cases of our series were associated at one time or another with other forms of arrhythmia.

6. As regards treatment, rest and digitalis restore many to normal rhythm. The use of quinidin sulphate is still in the experimental stage. Some few patients are not influenced by treatment, and the condition persists for years.

CONCERNING THE WASSERMANN TEST IN ITS RELATION TO PRENATAL AND CONGENITAL SYPHILIS.

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The student of medical history, and even the casual observer, cannot fail to be impressed with the fact that it moves, as it were, in cycles.

In the early days it might be said that the efforts of the physician were focussed, to a greater or less extent, upon the description and classification of the signs and symptoms whereby disease might be recognized. Following this might be said to have come the epoch of therapeutic endeavor directed toward the elaboration of methods of treatment; while the present age is avowedly that of preventive medicine, its aim and object being to forestall, anticipate and prevent the occurrence of disease in general in so far as this may be attainable.

It is inevitable that with such an end in view attention should be attracted and, to a large degree, focussed upon syphilis as one of the most generally distributed and far-flung infections to which the human race is subject; and of all the ramifications of this disease there is none of greater importance nor demanding more study than that which concerns itself with the prenatal and congenital phases of syphilis.

It is also inevitable that no consideration of the incidence of syphilis can be undertaken without a discussion as to the value and applicability of the Wassermann test as a means of diagnosis.

The introduction of the complement-fixation reaction as a means of diagnosis was undoubtedly a most valuable contribution to the elucidation of the study and treatment of syphilis, but like many other methods of laboratory investigation its usefulness can be enhanced or nullified in accordance with the skill with which it is employed and the acumen exhibited in its interpretation.

It is obviously essential that the complexities and niceties of

technic inherent in the reaction should be thoroughly and intelligently comprehended by those applying it; and it is equally, and perhaps even more, essential that a full and complete understanding of its limitations should be had by those charged with its interpretation, for, after all, the value of any method of examination, clinical or laboratory, rests mainly upon its interpretation in connection with and in terms of the particular patient.

Schleiter[1] emphasizes this when he calls attention to a prevalent tendency "to order a number of investigations by the laboratory, which may often be uncalled for, in the expectation that they will, in some mysterious manner, whisper the correct diagnosis"; and reiterates the important and, it would seem, obvious fact that "the physician owes it to himself to have a clear understanding of the laboratory procedures he calls to his aid—their principles, sources of error and when they are are not applicable to a given case."

In no procedure are these requirements of more importance than in the clinical application and interpretation of the Wassermann test, and in few instances are more care and skill required in the proper evaluation of the results obtained than when it is used as a means for the detection of prenatal syphilis.

The importance of syphilis as a cause of fetal death and of the pathologic sequences following birth is well known and often commented upon.

A most careful, extensive and masterly study of the value of the Wassermann reaction in obstetrics as a means to the diagnosis of prenatal syphilis is that of Williams,[2] which brings out the fact that 26 per cent of all fetal deaths between the end of the seventh month of pregnancy and the first two weeks following delivery are due to syphilis.

These statistics agree with those of other observers and are corroborative and illustrative of the widespread incidence of this disease and furnish a sufficient reason for the present concentration of attention upon it by all who are interested in preventive medicine.

Obviously the first step toward the prevention of any disease is its detection and the subsequent handling of the sufferer in such a fashion that he shall not furnish a source from which it may be transferred to others, and there are a few instances in which this is of greater importance and more promising of ultimate success than in the problem presented by prenatal and congenital syphilis. Competent observers have shown that if the presence of early syphilis is recognized a large proportion of infants otherwise doomed to the evils of inherited syphilis can be brought into the world free of infection; or, certainly, if this cannot be fully attained they

[1] Laboratory Diagnosis, Pennsylvania Med. Jour., 1921, **25**, 77.

[2] The Value of the Wassermann Reaction in Obstetrics Based upon a Study of 4547 Consecutive Cases, Bull. Johns Hopkins Hosp., 1920, **21**, 356.

can be so treated that their ultimate destiny as healthy citizens can be fulfilled.

Following the introduction of the Wassermann reaction, it was, naturally, largely depended upon to furnish the requisite diagnostic information. Unfortunately, as has been succinctly said:[3] "A product of our modern methods of diagnosis and treatment (of syphilis) is the pseudosyphilographer. To him the clinical study of syphilis is unnecessary. The public Wassermann laboratory makes the diagnosis without charge and a few injections of arsphenamin clear up the lesions." This, though a severe indictment, is too often true.

The Wassermann reaction as a routine method of investigation in obstetric cases is coming more and more into general use; the interpretation of the results obtained, however, for reasons not always easily explainable, presents in general a greater difficulty than in cases of acquired syphilis or of congenital syphilis investigated in later childhood.

A frequent method of utilizing the reaction in obstetrics is to apply the test to the cord blood, because this does not necessarily inform the patient of the nature of the investigation pursued and because the test is easily made without incurring the objections or refusal of the patient to submit to it.

The results of series collected, however, present great difficulties in the way of interpretation.

Williams[4] in 4000 mothers serologically examined obtained a positive Wassermann in 11.2 per cent, and draws the conclusion, from an analysis of the results obtained that a positive Wassermann on the part of the mother during pregnancy does not inevitably mean that the child will be syphilitic, as in only 57 of the 169 children concerned—all of Wassermann positive and untreated mothers—were clinical or anatomic evidences of syphilis elicited.

In Wassermanns made on the fetal blood at the time of birth, 38, or approximately 1 per cent, positives occurred; 29 of these cases were later investigated, some as late as three years after, with the following results: 17 developed definite evidence of syphilis; 5 showed no signs except a continued positive Wassermann; 7 showed no signs with a negative Wassermann.

A similar investigation of children whose Wassermann was negative at birth, however, showed 10 whose Wassermann was later positive, and he therefore states that "In view of these findings a positive Wassermann at birth does not imply that it will remain so, and, conversely, a negative Wassermann at birth does not necessarily mean that it may not become positive later." He therefore concludes that the information obtained by the

[3] Smith, C. M.: Treatment of Early Syphilis, Arch. Dermat. and Syph., 1921, 6, 723.

[4] See note 2.

Wassermann made upon the fetal blood at birth is not commensurate with the time and money employed in such an investigation.

It is, of course, to be recognized that even though the results of the Wassermann tests upon cord blood are apt to be at times fallacious and are always to be carefully and conservatively interpreted, still when taken in conjunction with the history and a careful examination, together with, if possible, an intelligent. "follow-up" in a certain proportion of cases, information of definite value may be obtained, and in any serious effort toward the eradication of any disease no means of even slight promise should be neglected.

We have come to realize that the Wassermann test is not infallible, and it is unfortunate that so much emphasis has been placed upon it as to give rise to a distorted idea of its value. It should be unceasingly reiterated that the meaning of a Wassermann reaction depends very largely upon the particular technic and degree of care with which it has been performed, and, further, upon an equal care in its interpretation and correlation with the patient. In any case, where properly checked and controlled, a positive Wassermann may be taken as very strongly presumptive evidence of the presence of syphilitic "reagin" in the blood.

Of great importance is the fact brought out by Thaysen[5] that unaccountable variations in the strength and even in the occurrence of the Wassermann reaction may take place in untreated cases of known syphilis. This is illustrated in Williams's series by 3 cases in which Wassermann-positive mothers who gave birth to syphilitic children, though untreated, gave a negative Wassermann some weeks or months later. Until we know more about the mechanism and *modus operandi* of the reaction this phenomenon cannot be satisfactorily explained. If, as has been tentatively assumed, the substance or substances giving rise to the reaction are lipoidal and connected with the lipoid metabolism of the body it is a possible presumption that they might be present in varying amounts at varying times in accordance with the reaction of the body to the infection; or, again, a possible explanation may lie in the so-called "selective action" of the reacting body in the presence of a series of antigens of similar type, all of which, until a further understanding of the reaction is had, must be purely hypothetic.

The ideal method of investigation in obstetric cases would, of course, imply a serologic examination of the child, and of both parents as well as a repetition of the tests later when indicated in conjunction with a careful and painstaking history and examination. This, of course, is rarely feasible.

Williams also emphasizes the importance of a routine microscopic examination of the placenta for the so-called Fränkel's disease,

[5] Spontaneous Variations in the Strength of the Wassermann Reaction, Acta Med. Scandinav., 1921, **55**, 281.

upon the presence of which he places great reliance as an evidence of syphilitic infection.

It seems not untimely to mention here what should be obvious, and yet what, in these days of laboratory tests galore, is sometimes overlooked—the exceeding value of a careful, keenly taken history, the importance of which in the diagnosis of syphilis is well emphasized by Broeman.[6]

The complete cycle of the ideal examination outlined above is, unfortunately, infrequently possible, but that some investigation should undoubtedly be made is indisputable, and the most feasible in the long run is the routine examination of the fetal blood with a full realization of the inherent fallacies of the method.

That such a method is not entirely without value is evidenced by the literature. Campbell[7] in a series of 34 latent cases reports 82.3 per cent of positive reactions.

Jeans and Cooke,[8] correlating the results of cord Wassermanns and placental studies with the results of Wassermanns made from six to nine months later, found a correspondence of 63.3 per cent of cord Wassermanns as compared to 27 per cent of placental examinations.

Ross and Wright[9] note the fact that congenitally syphilitic babies tend to give a negative Wassermann until a month or so after birth, and state that whether a positive Wassermann reaction with the cord blood is indicative of syphilis in the mother and *not* in the child, as believed by Fildes, or in the mother *and* the child, as held by Kolmer, the occurrence of 3.5 per cent of positives independently obtained by two observers is highly suggestive and warrants the use of the method.

Fordyce and Rosen[10] agree with Williams as to the inexpediency of cord Wassermanns and call attention to the fact that syphilitic babies, positive at birth, may later be negative and, still later, again positive. They feel, also, that a cholesterin plus only Wassermann in the mother before delivery requires corroboration, and state that in their experiences this type of reaction may occur in normal women during pregnancy.

Kolmer[11] [12] believes that the Wassermann on the cord blood

[6] A Thorough History an Important Factor in Syphilis, Am. Jour. Syph., 1921, **5**, 565.

[7] Pathologic and Public Health Aspects of the Diagnosis of Syphilis, Acquired and Congenital, in the First Year of the Disease, Public Health, London, 1921, **7**, 13.

[8] The Incidence of Hereditary Syphilis, Am. Jour. Dis. Children, 1921, **22**, 402.

[9] The Incidence of Congenital Syphilis among the Newly Born, Lancet, London, 1921, **1**, 321.

[10] Treatment of Antenatal and Congenital Syphilis, Arch. Dermat. and Syph., 1922, **5**, 1.

[11] Prenatal Syphilis with a Plea for its Study and Prevention, Am. Jour. Dis. Children, 1920, **19**, 344.

[12] Immunity to Syphilis, with Special Reference to Congenital or Prenatal Syphilis, Arch. Pediat., 1920, **37**, 129.

alone cannot be relied upon to always give complete information, and notes the value and applicability of the luetin test to the problem.

That there is a difference of opinion as to the expediency of the cord Wassermann is evident, but, at all events, if, as is frequently the case, this is the only avenue of investigation available, it seems questionable whether or not it should be entirely neglected.

This is the method which has been employed in the routine investigation of obstetric cases in the Pittsburgh Hospital in a series of 269 cases, and the results of the series, though too small to be of great value or significance, are reported on the principle that, as the Scotch say, "Many a mickle makes a muckle."

The method employed follows:

Serums. These were collected from the cord immediately after delivery; the serums were separated and inactivated for fifteen minutes at 56° C. immediately before the test. Practically all serums were tested within twenty-four hours of their collection and used in dose of 0.2 cc.

Amboceptor. Glycerinated amboceptor, diluted with normal salt solution according to titer, and used in a constant dose of 0.1 cc.

Complement. Diluted 1 to 10 with normal salt solution and titrated immediately preceding the main test in the presence of 0.1 cc of amboceptor and 0.5 cc of 2.5 per cent suspension of sheep cells.

Antigen. A triple battery was always used, consisting of cholesterinized (0.4 per cent) extract of the human heart, acetone insoluble lipoids of the human heart and alcoholic extract of syphilitic liver. The dose was always from five to ten times the antigenic amount, and this amount was always from five to twenty times less than the anticomplementary unit.

Preliminary incubation was for one hour in an ice-water bath at 4° to 6° C., after which the rack was placed in the 38° C. bath for five minutes, removed, amboceptor and sheep cells added and returned to the 38° C. bath for thirty minutes, or until all controls were hemolyzed.

The usual controls, including a known positive and negative, were always included.

This technic has been carefully checked and is believed to give reliable results.

In 269 cord bloods so tested there were 227 negative reactions and 28 anticomplementary serums.

There were fourteen cases in which a positive result was obtained, an incidence of 5.1 per cent.

In every case in which a positive reaction was obtained a Wassermann was made upon the mother and, whenever possible, upon the father, and an effort made to obtain any history of value in corroborating the test.

The results of the investigations are shown in the following table:

	Cord blood Wassermann.	Wassermann of mother.	Wassermann of father.	History and remarks.
1.	$C+^4A+^4S+^3$	Negative	Not obtained	None elicited.
2.	$+^4\dagger$	....	Not obtained	Five miscarriages.
3.	$C+^4A+^4SO$	Negative	Not obtained	None elicited.
4.	$+^4$	Negative	Not obtained	None elicited.
5.	$+^4$	Negative	Negative	None elicited.
6.	$+^4$	Negative	Not obtained	None elicited.
7.	$+^4$	Negative	Not obtained	None elicited.
8.	$+^4$	$+^4$	Negative	Spinal; colloidal gold 5555100000; patient has paresis.
9.	$+^4$	Negative	Negative	None elicited.
10.	$+^4$	Negative	Not obtained	One abortion; one stillbirth.
11.	$+^4$	Negative	Not obtained	None elicited.
12.	$+^4$	Negative	Not obtained	None elicited.
13.	$+^4$	Negative	Not obtained	None elicited.
14.	$+^4$	Negative	Anticomplementary	One abortion.

C = cholesterinized extract; *A* = acetone insoluble lipoids; *S* = syphilitic liver extract.

$\dagger+^4$ = plus 4 in all antigens.

For various reasons, mainly because most of the patients were private cases, no satisfactory "follow-up" was possible, and the possible results of serologic examinations, if made later, is purely speculative. Despite this fact, and regardless of the further fact that in many instances the history leaves much to be desired, data corroborative of the Wassermann were obtained in 3 of the 14 cases, or approximately 30 per cent, findings which would seem to warrant a continuance of the method.

Conclusion. These results, in a small way, are in agreement with those of more extensive investigations, and seem to warrant the conclusion that the results of cord Wassermanns are not to be unreservedly relied upon when taken alone, and should not be made the sole basis for a diagnosis of syphilis. If the subject of prenatal and congenital syphilis is to be the object of a concentrated attack, it is obvious that serologic investigations must be extended to include not only both parents but also the child at birth, and in later infancy when the results of Wassermann reactions are apt to be more truly indicative of the presence or absence of luetic infection.

TWO INSTANCES OF DEFECTIVE INTERVENTRICULAR SEPTUM OF THE HEART.

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The congenital anomalies of the human heart due to defective development are of many kinds and have been described by many observers. Some of them are rarely detected during life, either because no symptoms are produced by the defect or because the distinctive symptoms and signs are encountered so infrequently that they are not familiar to the clinician.

The two cases to be described have to do with defects in the interventricular septum, and although both were congenital, one produced no symptoms whatever and the other caused symptoms, signs that were supposed to be due to an open ductus Botalli.

In the sections devoted to congenital heart disease in Osler's *Modern Medicine*, volume IV, contributed by Abbott, defects in the interventricular septum were found in 161 of the 412 cases studied, and in 149 of these the defect was situated in the membranous portion and in 12 in the muscular portion of the septum. In the first case to be described here the defect was located at the base, but in the second case it was in the muscular portion of the septum. Since the publication of the article by Abbott[1] but one similar case can be found, the one reported by Meyer[2] in 1914.

Case I.—C. B., female, aged twenty-three years, single.

Family History. Father alive and well. Mother dead, cause unknown. One brother died at seven years with heart disease, which began when he was one year old. He was cyanotic. Five other children died of pneumonia and croup.

Past History. Whooping-cough at the age of four years. No history of any other illness.

Present Illness. This began when she was six years old and continued until her death. The first sign noticed was cyanosis and the first symptom shortness of breath on exertion. Her condition became aggravated as time went on and the shortness of breath became so severe that she would often stagger and fall on the street. After a rest of a few minutes she would be able to proceed. The dyspnea finally became so acute that she entered the hospital, and while there she developed a fever due to sepsis, of which she died.

Physical Examination. The patient was short in stature and diminutive in size. The lips, finger-tips and ears were cyanotic

[1] Osler's Modern Medicine, 1908, **6**, 355.
[2] Jour. Anat. and Physiol., London, 1913–14, **48**, 123–127.

and the cheeks had a mahogany flush. The fingers and toes were clubbed. After the slightest exertion there was dyspnea. There was no edema.

The heart, at the apex, had a diffuse impulse which could be felt 0.5 cm. to the left of the midclavicular line. A continuous thrill could be felt at the junction of the third costal cartilage and the sternum. By auscultation a murmur could be heard which continued through systole and diastole. It was heard best in the second left intercostal space and along the left border of the sternum to the apex. The pulse-rate was 80 and the rhythm regular.

FIG. 1.—Case I. Defect in the membranous portion of the interventricular septum, showing vegetations in one leaflet of the aortic valve.

The chest was poorly developed, the anteroposterior diameter diminished and there was retraction above and below the clavicles. The breath sounds were normal.

The liver was a trifle enlarged, the dulness extending from the fifth rib to 2 cm. below the costal margin, where the edge could be felt.

Clinical Diagnosis. Septic endocarditis. Probable patent ductus Botalli.

Postmortem Examination. The body of a slightly built woman, 5 feet 2 inches tall. There was a small amount of edema of the feet and legs. Marked cyanosis of the lips, face, hands and feet. The pupils were slightly dilated. There was no lymphatic enlargement.

The peritoneal cavity contained about 500 cc of dark-colored fluid. In all other respects the peritoneum and its contents were normal.

The Heart. The pericardium was free from adhesions and the fluid was excessive. The heart itself was enlarged and measured 13 x 12 x 7 cm. The enlargement was due to distention of the right auricle and hypertrophy of the right and left ventricles. The left auricle was small. When the chambers of the heart were opened the right ventricular wall was hypertrophied and equalled in thickness the wall of the left ventricle, while the wall of the right auricle was so hypertrophied that it equalled in thickness the ventricular walls. The mitral and tricuspid valves were normal. The orifice of the pulmonary artery was noticeably diminished in circumference and its valves thickened. On one cusp of the aortic valve there were extensive vegetations, in the smears and cultures of which the Staphylococcus aureus was found.

In the interventricular septum, just beneath one leaflet of the aortic valve, was an aperture 1.5 cm. in diameter, which opened on the right side just beneath the adjacent leaflet of the pulmonary artery. It was oval in shape and was bounded laterally and above by a thin membranous tissue and beneath by the cardiac muscle. On account of this defect there was an arteriovenous communication between the ventricles.

The lungs showed no abnormality except an old organized infarct on a posterior lower margin. The spleen was somewhat enlarged. It measured 15 x 7 x 5 cm. The pulp appeared congested and swollen. The uterus was infantile. The remainder of the examination revealed no abnormality and is omitted.

The microscopic examination of the tissues confirmed the gross findings.

Diagnosis. Congenital defect of the membranous portion of the interventricular septum. Acute vegetative endocarditis. Old infarct of the lung.

CASE II.—J. D., aged thirty-seven years. Complains of nervousness and weakness, loss of appetite, sleeplessness and shortness of breath on exertion.

Family History. Unimportant.

Past History. Has had the usual diseases of childhood. No history of any venereal infection. Has drunk to excess and taken no care of himself at all.

Present Illness. Began two days ago with the symptoms described above. He is very nervous, unable to keep quiet. Keeps jumping out of bed and sees things at night. His speech is thick and there is a marked tremor of the hands. He is continually picking at the bedclothes.

FIG. 2.—Case II. Funnel-shaped depression in the muscle of the interventricular septum with an opening into the right ventricle at its upper margin.

Physical Examination. The face and body appear much congested. The tongue is coated and tremulous. The pupils are midwide and equal and react to light and accommodation. The throat is clear. In the lungs there are no rales or dulness. The vesicular resonance of the left lung is diminished on account of the enlargement of the heart.

The heart dulness is much increased to the left. There is no thrill. There is a rough systolic murmur at the apex which is transmitted to the back and heard at the angle of the scapula. The liver can be felt three inches below the costal margin. The edge is smooth.

The mental condition is clouded. The patient is delirious. The superficial and deep reflexes are exaggerated. The cranial nerves are intact. The remainder of the examination reveals no abnormalities.

Diagnosis. Delirium in potu. Mitral regurgitation.

Postmortem Examination. The subject is a fairly well-nourished man. The pupils are midwide and equal. The lips and mucous membranes are pale. There is no edema of the extremities.

The peritoneum and the organs within its cavity are normal except for a chronic obliterative appendicitis.

The heart is covered by a smooth pericardium in which there is no excess of pericardial fluid. It measures 13 x 9 x 7 cm. When opened, the left ventricular wall is 2 cm. in thickness; the right is not hypertrophied. The mitral leaflets are somewhat thickened and the valve incompetent.

The papillary muscle extending to one leaflet of the tricuspid valve is fused with the columnæ carneæ and has caused a shortening of the chordæ tendineæ, rendering the valve incompetent. This makes one leaflet short while the remaining two appear lengthened in comparison. In the interventricular septum on the left side there is a depression measuring 4 x 2 cm. and 1 cm. in depth. There is a corresponding depression into the right ventricle. Near the upper margin of the depression, on the left side of the septum, there is an opening 4 mm. in diameter which communicates with the cavity of the right ventricle. The appearance is similar to a funnel pointing toward the right ventricle. On the left side the walls of the depression are composed of muscle, but on the right side there is dense fibrous tissue about the opening. No other abnormality of the heart is found.

The lungs are crepitant but present a congested appearance, particularly in the lower lobes, presumably due to hypostatic congestion. The right lung is adherent to the diaphragm.

The spleen measures 20 x 12 x 4.5 cm. It is firm in consistency, and on section the pulp appears increased in amount.

The liver is roughened by nodules on its surface, which vary in size from a pin-head to a pea. It has a mottled reddish color and its consistency is firm. On section it cuts with resistance and the connective tissue is distinctly increased. The remainder of the examination reveals no abnormalities.

Microscopic Examination. Microscopic examination of the tissue about the defect in the septum shows no evidence of any inflammatory reaction. Sections from the lung show the bronchi packed with polynuclear leukocytes and the alveolæ filled with red blood cells, polynuclear leukocytes and blood serum. The sections from the spleen show a marked increase in the blood content of the pulp with a diminution in the size of the Malpighian bodies. The liver contains a great increase in the interlobular

connective tissue with compression of the lobules. The liver cells are fatty. In the interlobular connective tissue are many long vessels lined with low epithelium which are taken to be bile capillaries. These are frequently surrounded by large accumulations of lymphocytes.

Diagnosis. Tricuspid insufficiency due to obliteration of the papillary muscle, which is bound firmly to the ventricular wall. Relative mitral insufficiency. Interventricular septum defect through funnel-shaped opening. Chronic passive congestion of the lungs and spleen. Early bronchopneumonia. Cirrhosis of the liver.

Several theories have been advanced in explanation of the defects in the interventricular septum. We know that the interventricular septum is not complete in early fetal life, the defect being situated along the upper margin. It is due to the failure of the septum to complete its development that explains defects like the one described in Case I. Stenosis of the pulmonary artery and transposition of the pulmonary artery and aorta are frequently found coëxisting with the interventricular septum defect. In the case of these multiple anomalies opinion has been divided upon the question of which was the primary one.

Meckel believed that the defect in the septum was primary and that the diversion of blood through it led to a stenosis of the pulmonary artery from disuse. Hunter and Morgagni were of the opinion that pulmonary stenosis in fetal life was the primary cause; the increased pressure in the right ventricle produced by the stenosis prevented the septum from closing.

In the Hunterian Lectures of 1909, Keith was of the opinion that faulty fusion of the bulbis cordis and incomplete development of the infundibulum played an important role in explaining the congenital anomalies of the heart. A large number of the instances of pulmonary stenosis are due to incomplete expansion of the infundibulum after the bulbis cordis has fused with the right ventricle. In 80 to 90 per cent of the cases of pulmonary stenosis that Keith has seen there has also been a foramen in the interventricular septum. The interventricular septum closes under normal conditions in the second month of fetal life, and it is at this time that the infundibulum expands and opens up so that both the stenosis of the pulmonary artery and the incomplete closure of the septum might be due to incomplete development of the infundibulum. This theory of Keith's does not explain the septum defects that occur without any other coëxisting anomaly.

The symptoms produced by defects in the interventricular septum depend a great deal on the location of the defect, its size and whether it is accompanied by other cardiac anomalies. With uncomplicated defects in the region of the membranous portion of the septum there may be no symptoms whatever. In such

cases the individual may reach middle life without suffering any ill-effects. The same is true of small defects in the lower portion of the muscular septum as in Case II. Where the defects are large, and particularly if other anomalies are present, cyanosis and dyspnea are the rule. Attacks of syncope following any exertion as described in Case I are not uncommon. These patients are prone to develop infections, particularly endocarditis and pulmonary tuberculosis.

The physical signs resulting from defects in the septum are described in detail by Abbott.[3] They are most intense over the central portion of the precordium, over the third and fourth ribs, just to the left of the sternum, because the septum is situated here. In brief there is usually hypertrophy of the right ventricle, and in the case of large defects precordial bulging and visible pulsation. A thrill can be felt directly over the septum, sometimes over the entire precordium. Murmurs, systolic as a rule, can also be heard best in this region and are not transmitted to the vessels of the neck. The intensity of the murmur is not always commensurate with the size of the defect.

On account of the interchange of blood between the two ventricles there is usually cyanosis. Hippocratic finger-tips and polycythemia are common accompaniments of the condition.

The two cases reported here are typical examples of congenital interventricular septum defects. Case I is an instance of multiple defect, being accompanied by pulmonary stenosis. This is a common combination and is attributed, according to the more recent theory of Keith, to an incomplete development of the infundibulum cordis. The defect in Case II is believed, in the absence of all signs of inflammatory reaction, to be congenital and due to incomplete development. By reason of its location it must be classed among the rare anomalies of the septum. The causes of developmental defects in this location are not understood.

THE TREATMENT OF HYPERTOXIC CASES OF TYPHOID FEVER BY TRANSFUSION WITH RECENTLY ARTIFICIALLY IMMUNIZED BLOOD.*

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It is with a certain degree of temerity that I approach another discussion of so hackneyed a subject as typhoid fever. Since the

[3] Loc. cit.

* Read before the District of Columbia Medical Society, November 30, 1921.

introduction of the name "Fièvre Typhoide," by Louis,[1] in 1839, medical literature has been flooded with publications on this subject. A review of this literature is at once inspiring and instructive. No better example of scientific medical progress can be found in all history. Rational therapy depends upon an accurate differential diagnosis, and, in this instance, there is a striking example of the evolution of modern diagnostic methods; that is, the correlation of bedside observation and clinical experience and the more accurate laboratory methods.

It is not within the scope of this paper to review in detail the history of typhoid fever, with the exception of the progressive steps in the methods of treatment, especially specific therapy. However, one cannot pass without recalling a few of the salient facts in history to which are attached the names of the pioneers in this field.

Although this discussion is particularly in the interest of the treatment of typhoid fever along specific lines, and not those of a symptomatic nature, a few outstanding facts in the development of our ideas of the treatment of this disease cannot be ignored. No consideration of treatment would be complete without mentioning methods of prevention. This can be briefly discussed under three heads: (1) It might be possible to immunize all individuals; however, this immunity is not permanent and is only relative and might be overcome by a massive infection. (2) The destruction of all the organisms in the excreta, but this method offers the difficulty of discovering all carriers and the mild undiagnosed cases. (3) The protection of all foods and water by proper hygienic measures. Since none of these methods is flawless they are all of equal importance.

The rather unimportant role of drug therapy hardly merits discussion here. The introduction of a high caloric diet marks one of the great steps in advance in the treatment of typhoid fever. It has been shown by Coleman and Du Bois[2] that a diet rich in carbohydrates maintains a nitrogen equilibrium best and prevents the great emaciation so often seen, and perhaps the cause of death in many cases. This conception of the dietary management of typhoid patients may be regarded as of equal importance with any other step forward in the conquest of this disease.

The judicious use of hydrotherapy is an important one, water being used both internally and externally. Of historic interest only is the Brand method of putting the patient in a tub bath at 65° F. Although heralded by Brand[3] as the ideal method of rapidly reducing the hyperpyrexia, it was found to be fraught with many dangers and has been generally discarded.

The use of typhoid vaccine as a therapeutic agent has been the source of many clinical experiments and reports. Fraenkel[4] was the first to use the vaccine by the subcutaneous method, followed

by Collison,[5] Krumbhaar and Richardson,[6] Zupink, Müller and Leiner,[7] and many others. They all report a reduction in the mortality and the length of the disease. Working independently, Ichikawa[8] and Kraus and Mazza[9] introduced the intravenous method with very striking results. Many cases showed a fall of temperature by crisis, and the duration and severity of the disease were materially reduced in many others. It was soon discovered, however, that the same results could often be obtained with any foreign protein, as other bacteria, proteose, albumose, etc. It has also been observed that this method is not unattended with danger.

Labbe and Moussand,[10] following the original work of Letulle and Mage,[11] used colloidal gold solution by the intravenous route in the treatment of moderately severe and grave cases. They report a reduction in the general symptoms of infection and intoxication, shortening of the disease and a reduced mortality.

The use of a specific immune serum would seem the logical treatment of typhoid fever from the theoretic standpoint, and this has been the goal of many investigators. Numerous immune sera obtained from animals, especially horses and goats, have been used. Most of them have been reported with great enthusiasm by the originator, but only with fairly encouraging results by the subsequent observers. Chantemesse[12] prepared a serum by injecting horses with a soluble typhoid toxin. His therapeutic dose is a very small quantity injected subcutaneously, and only one dose is used. His results in 1000 cases were very encouraging, the mortality being reduced to 4.3 per cent, a very low average for Paris at that time. Besredka[13] produced a serum by injecting horses with the endotoxins obtained from dried cultures of typhoid bacilli. The observations of Besredka and the other workers along this line have not been of any practical value. Ludke[14] prepared an antiendotoxic serum from goats, and reports encouraging results. Garbat and Meyer[15] report favorable experimental results with serum obtained by injecting animals with sensitized typhoid bacilli, and other animals with untreated organisms, pooling the sera of the two. Rodet[16] and his co-workers report the most favorable results in the treatment of typhoid fever with specific serum. He immunizes horses with living bouillon cultures and endotoxins. The immune serum is given in repeated subcutaneous doses, the quantity varying from 10 to 20 cc. He reports a marked shortening of the disease and a rapid reduction of the height of the temperature. His results have been confirmed by Odilhan,[17] and Remond and Minvielle[18] and others. Stokes and Fulton[19] report a serum obtained by injecting hogs with increasing doses of bouillon cultures, producing a serum with an agglutination titer of $\frac{1}{450000}$. Its use in 23 cases showed favorable results.

Von Jaksch[20] (1895) was apparently the first to make use of the

immune serum of convalescents and the results obtained were very favorable. His work was confirmed a few years later by Walger[21] (1898). This fertile field of investigation, the use of immune human serum, remained untouched for almost ten years. Petrovitch[22] (1915) employed the serum of convalescent or immunized individuals in the treatment of 500 cases with a mortality of 4.3 per cent. In 1000 control cases treated without serum the mortality was 12.8 per cent. He usually used about 10 cc intravenously. This was done in the Serbian army.

Koenigsfeld[23] reports some very interesting experiments in the treatment of typhoid fever with the patient's own serum. He gives daily intravenous injections of serum in doses of 2.5 to 4 cc. In 26 cases treated there was a marked improvement characterized by a reduction of temperature, shortening of the disease, improvement in the sensorium, and especially good results in the comatose cases. These finding were confirmed by Meyer.[24]

The use of immune blood or blood serum from convalescents in the treatment of infectious diseases is by no means a new procedure. It has been attempted in a great variety of conditions. Scarlet fever has been treated by injections of blood serum and whole blood from convalescents, both subcutaneously and intravenously, with especially good results in the very toxic cases, as reported by Weaver.[25] The recent epidemics of influenza found many adherents of serotherapy, convalescent serum and whole blood being used intravenously. Favorable reports were made by Stoll,[26] and O'Malley and Hartman,[27] but the general consensus of opinion was not so encouraging. When it is remembered that the pneumonia complicating the influenza was the result of a secondary invader and that this secondary infection varied with the individual and the locality, the serum or blood in this instance cannot be properly classed as specific. Very recently convalescent serum has been used as a prophylactic and therapeutic agent in measles, and the results reported from Germany are exceedingly encouraging. Many other examples of attempted specific therapy using convalescent serum could be enumerated. However in none of them has it been possible to demonstrate any appreciable amounts of protective antibodies.

Typhoid fever presents an entirely different problem. By means of the well-known Widal reaction it is possible to demonstrate the agglutination titer of the serum. While there are probably many different protective antibodies in the circulating blood, this is our only index. The Widal reaction is present for a relatively short time in low dilutions after convalescence, and for a longer period and in much higher dilutions after artificial immunization. Nevertheless the immunized individual, both convalescent and artificial, shows great resistance to infection long after the disappearance of the agglutinins, especially the convalescents. This clearly

indicates that there is a cellular immunity in addition to the circulating or humoral immunity. *The great excess of the circulating immune bodies in the artificially immunized is of great practical importance in the serotherapy of typhoid fever.*

The previous attempts at specific therapy in typhoid fever, using immune human serum, as mentioned above and reported by von Jaksch,[28] Walger,[29] Petrovitch,[30] and Garbat,[31] failed to appreciate the quantitative differences in the antibody content of convalescent and artificial immune serum. In most of the cases only convalescent serum was used. When one remembers that many convalescent sera show a very low agglutination titer, and occasionally none at all, it is not surprising that these earlier results were not regarded with any great enthusiasm. In the few instances in which artificial immune serum was used very little regard was paid to the length of time after immunization, so that the serum was not obtained at the peak of the antibody content. Furthermore, very small doses of serum were used. This was, of course, a necessity in dealing with convalescents. However, the passive immunity conferred must have been comparatively small.

The present method is attempted in the light of modern theories and experiences in immunity as especially related to typhoid fever. To summarize these very briefly: The immunity produced through infection by the Bacillus typhosus (or the para A and B) shows a very high cellular immunity but a relatively small content of circulating antibodies, the latter rapidly disappearing during convalescence. The immunity produced by prophylactic inoculations shows a very high content of circulating antibodies, disappearing rather slowly, and a relatively low cellular immunity. The index of circulating antibodies is the agglutination titer, no other satisfactory one being available, although it must be realized that the agglutinins represent only one of a number of protective substances.

If the foregoing hypotheses be true, and experience and experiment point in that direction, then the use of blood from recently artificially immunized individuals would seem to be the proper procedure, especially in the very toxic cases. On theoretic grounds the use of whole blood in large quantities offers many advantages. The larger quantities (500 to 700 cc) furnish a great amount of protective substances. The inclusion of the cellular elements of the blood furnishes additional coagulating properties, much needed leukocytes and the red blood cells combat the anemia and emaciation and stimulate the bone-marrow, thus aiding red and white blood cell formation. The use of the large quantity of blood also obeys the well-established rule of serotherapy that an excess of serum should always be employed.

The following two cases are then presented in the way of a preliminary report in support of these theories:

CASE I.—E. W. T., male, aged thirty-six years; occupation, clerk.

History. The family history was negative. He had measles and mumps as a child. In 1906 he had a continued fever lasting three weeks, which was said to be typhoid fever, but without laboratory confirmation. He is a great user of tobacco, both smoking and chewing. For the past eight years he had been a constant user of alcohol, consuming about one pint of whisky daily and occasionally a larger amount. He is married and has three healthy children.

The patient was first seen on June 4, 1921, by Dr. E. W. Birch. For two weeks he had been complaining of a moderate malaise and headache, and there had been a nose-bleed one week previously. A specimen of blood taken on June 5 and reported on June 6 showed a positive Widal with the Bacillus typhosus. The patient resided at Fort Meyer Heights, Va., a suburb of Washington, but there had been no other cases of typhoid fever in the immediate vicinity. The well-water on this place showed no fecal contamination and no other members of the family were affected. It was later learned that the patient was very fond of raw oysters and had eaten them frequently during the previous month. On June 7 he was removed to the Sibley Hospital.

June 7 to June 19. The temperature on admission was 104.4°. During this period of twelve days there was practically a continuous temperature, with a minimum of 102.6° and a maximum of 104.6° by the axilla. He was constantly irrational and semicomatose.

June 20 to June 25. During this period of six days the diurnal temperature variations were greater, with a minimum of 99° and a maximum of 103.6°. The delirium and semicoma continued. On June 25, the twenty-second day of the illness, there was a profuse intestinal hemorrhage, accompanied by rapid pulse (160 per minute), pallor, rapid sighing respirations, sweating and collapse. There were no symptoms of perforation. Dr. Thomas A. Claytor saw the patient in consultation and advised blood transfusion, although he gave a very poor prognosis. The writer then saw the patient for the first time for the purpose of transfusion. 600 cc of blood was given by the citrate method, with a very rapid and marked improvement. The blood-pressure before transfusion was 100 mm. and afterward was 108 mm. systolic. The temperature fell to 98° after the hemorrhage, but by the next day was 103.6°.

June 26 to July 4. During this period of eight days following the transfusion the condition of the patient was fairly good. The temperature varied between 100° and 104.2,° with a continuation of the delirium.

July 3 a small quantity of food was given by mouth, the first since the hemorrhage. This was followed by a profuse intestinal

hemorrhage. A transfusion of 700 cc was again given (thirtieth day of illness). The symptoms of collapse present after the first hemorrhage were again in evidence, and were as rapidly and effectually ameliorated by the transfusion.

July 5 to July 7. The temperature continued high after the second transfusion, and for this period of three days varied between 100.8° and 104.° However the patient's general condition was not very satisfactory. The delirium was more marked, alternating with periods of complete coma. The emaciation was extreme, and there was a very rapid and shallow pulse. In view of the poor condition of the patient and the catastrophe following the ingestion of food after the first transfusion the writer suggested that another transfusion be given in place of food. It was realized that 600 or 700 cc of blood represented more food than this patient could take in by mouth for quite a few days, that the normal blood might contain some natural protective substances, and, fortunately, there were plenty of donors available. Therefore on July 7 (thirty-third day of disease) a transfusion of 700 cc was given. There was no reaction and the only result of this treatment was some improvement in the patient's general condition. The temperature curve showed no essential changes.

July 8 to July 15. The temperature for this period of seven days following the third transfusion of normal blood varied between 99.6° and 104°. There was no abatement of the very toxic symptoms as enumerated above. Both nurses on the case had offered to be donors, and since both had been artificially immunized when beginning duty on this case it was deemed advisable to try the effect of transfusion with recently immunized blood. Only one of the bloods was found to be in the proper iso-hem-agglutinin group. The Wassermann was negative and the serum was found to have a very high agglutination titer (typhoid, $\frac{1}{12000}$; paratyphoid A, $\frac{1}{7000}$; paratyphoid B, $\frac{1}{5000}$). She had received three doses of the Army Medical School triple vaccine, at one week intervals, and had received the last dose on June 23, 1921, so that this represented the twenty-first day after the last injection.

July 25. A fourth transfusion of 500 cc was given, but this time with recently artificially immunized blood. This was the fortieth day of the disease and the temperature was 103° just before the transfusion. There was no reaction.

July 16 to July 30. On the day following the fourth transfusion the maximum temperature was 100° and by the following day it was 99.2°. During this period of fifteen days the temperature was practically normal, varying between 97.6° and 99.6°. The symptoms of extreme toxemia improved very rapidly. Whereas the temperature was practically normal within thirty-six hours of this transfusion the delirium had practically disappeared in forty-eight hours. The pulse and respirations also showed a proportionate

improvement. From this time up to July 30 the condition was one of steady improvement. Food was again allowed in the middle of this period.

July 31 to August 13. On July 31, the fifty-eighth day of the disease, there was a recrudescence of the fever. For the next fourteen days it varied between 99.8° and 101.4,° but there was no return of the delirium, coma, rapid pulse or other toxic symptoms, and the patient continued to take his food without mishap.

August 14 to August 28. This period of fourteen days marked one of steady improvement. The temperature remained normal with the exception of an occasional rise to 99.° He was discharged from the hospital on the eighty-sixth day of the disease.

After a rest of about one month at home he has returned to his work. Upon questioning it is interesting to learn that he remembers nothing of his stay in the hospital until the middle of the first period of normal temperature, about four days after the fourth transfusion. He does not recall anything about the transfusions.

Laboratory Data. The Widal reaction done on June 6 and June 18 was strongly positive with the Bacillus typhosus. The leukocyte counts were as follows: June 6, 2900; June 17, 2200; June 23, 1900; June 28, 3600; July 1, 2700; July 6, 4700. It is interesting to note the rise of leukocytes following transfusion. The erythrocyte counts and hemoglobin estimations made before and after the first two transfusions are not included in this report, as there was some question as to their accuracy. Urine examinations were made at various periods of the case, and there were no pathologic changes with the exception of a faint trace of albumin and a few casts. Both of these disappeared during convalescence.

A summary of this case presents a few outstanding features: the value of transfusion in typhoid hemorrhage is clearly demonstrated in spite of the misgivings expressed in practically every standard text-book. The timeworn axiom that blood-pressure is raised and bleeding increased is a fallacious one, as the systolic pressure is usually only raised from 8 to 10 mm., certainly not enough to increase hemorrhage. The use of blood as a supportive measure and as food in such a case, where there is great inanition and where food is contraindicated, would seem to be of value. But the most striking feature is a comparison of the results of the four transfusions. Three transfusions of normal blood alleviated the symptoms of hemorrhage in two instances and acted in a supportive manner in a third, but the temperature and toxemia were in no way affected. The fourth transfusion of recently artificially immunized blood produced a prompt fall in temperature and a rapid disappearance of the symptoms of toxemia.

Case II.—A. L. G., female, single, aged twenty-six years, occupation, school teacher.

History. With the exception of mumps, measles, and chicken-pox in childhood the patient has never been ill. She has always been very robust and athletic. The family history is uninteresting. The last two weeks of August, 1921, were spent on a farm. On September 6, 1921, she complained of a dull headache and of general muscular pains. Home remedies were tried for several days, but as the symptoms did not disappear and there was an increasing stupor the writer was consulted.

September 9, 1921. The patient was a young woman, quite robust, and appearing very stuporous. A general physical examination was negative with the exception of a markedly coated tongue, tympanites and sluggish reflexes. The temperature was 103.8,° respirations 18 per minute, and the pulse 62 per minute, and slightly dicrotic.

September 10 to September 18. During this period of nine days the temperature varied between 101.2° and 104.6°. There was a gradually increasing stupor, but the patient could be aroused by persistent stimulation. The regimen consisted of sponge baths for hyperpyrexia and a high caloric diet. The blood culture, taken on September 14, was positive for the Bacillus typhosus.

September 19 to September 30. This period was marked by an almost continuous fever, varying between 103° and 104.8°. The stupor had now become complete and there was a delirium, sometimes of the low muttering type and sometimes very agitated. There had been no evidence of hemorrhage or perforation, but the emaciation was extreme. When the diagnosis of typhoid fever had been made all the members of the family had been given typhoid vaccine as a prophylactic. There were two brothers, one of whom was in the same iso-hem-agglutinin group as the patient. With the possibility of using his blood the intervals between his doses of vaccine were shortened to five instead of seven days. He had therefore received his last injection on September 20, 1921. The vaccine used was the triple vaccine of the U. S. Army Medical School. The agglutination titer of his blood serum was $\frac{1}{6000}$ for the Bacillus typhosus, $\frac{1}{3500}$ for Bacillus paratyphosus A and $\frac{1}{3000}$ for Bacillus paratyphosus B. In view of the increasing toxemia and emaciation 650 cc of the recently artificially immunized blood of the brother was given. The temperature just before the transfusion was 104° (September 30, the twenty-fifth day of the disease).

October 1. The patient's general condition is greatly improved. She is much more quiet, takes nourishment better and the maximum temperature was 102.2.°

October 2. The temperature on the second day following the transfusion was practically normal: maximum 99.2,° minimum 97.8°. There is a continuation of the general improvement and much less evidence of toxemia.

October 3. The temperature remained normal and the delirium had entirely disappeared. The patient would now answer questions by nodding the head. Aside from a tremendous asthenia all evidence of the profound toxemia had disappeared on the third day following the transfusion.

October 4 to October 29. This period was one of a slow convalescence. For the first week the temperature would occasionally reach 99.6.° The patient gradually gained weight and strength. When questioned she said that she did not recall the transfusion in any way, and, in fact, she had no recollection of anything from the fourth day after she went to bed until four days after the transfusion.

Laboratory Data. Blood culture on September 14 was positive for Bacillus typhosus. September 10: Erythrocytes 4,645,000, leukocytes 5600, hemoglobin 82 per cent (Dare). The following additional leukocyte counts were made: September 15, 4400; September 19, 2950; September 28, 2100; October 3, 4900. (Note rise of leukocytes after transfusion.) Widal reaction on September 20 and 29 were positive with the Bacillus typhosus. The Bacillus typhosus was found in the urine and the feces. Urine examinations were made at various times. There were no pathologic changes with the exception of a trace of albumin and a few leukocytes and casts, all of which disappeared during convalescence.

One aspect of the typhoid question that naturally presents itself is the question of the necessity for further developments in treatment when our present-day methods of prevention are so well advanced. A study of the available statistics shows that we have beguiled ourselves with a false sense of security. The most recent complete report is contained in the *Twentieth Annual Report of the Bureau of the Census, Mortality Statistics*, for 1919: "The number of deaths from typhoid fever in 1919 is 7860, corresponding to a death-rate of 9.2 per 100,000 population, which is much lower than the rate for 1918 (12.6), and is the record low rate in the period of twenty years from 1900 to 1919 inclusive. It is based on transcripts of death certificates received from the registration area for deaths, which in 1919 had an estimated population of 85,400,437, or 81.2 per cent of the total estimated population of the United States and the territory of Hawaii." It is safe to assume that the total deaths from typhoid fever in this year is about 10,000. The only available data for 1920 is contained in the ninth annual survey of the large cities (100,000 or more).[32] A study of this report shows a very slight general decrease in the death-rate, but even cities with very low averages show an occasional outbreak. The situation in 1921 does not seem to be so favorable. I shall quote from the *Statistical Bulletin*, Metropolitan Life Insurance Company, October, 1921:

"What is the significance of the remarkable increase in the number of deaths from typhoid fever during the months of August and September of this year? The first six months of the year closed without any indication of a check in the rate of decline for this cause of death. The figures for Metropolitan Industrial policyholders for the period January to June showed that there had been a decline of 14 per cent in the typhoid fever death-rate among white persons and 15 per cent among colored persons as compared with the rate of the first six months of last year. But the number of deaths during the third quarter of 1921 has been so large that at the present writing the typhoid fever death-rate for this year to date equals that of last year and is still rising. Unless there is a change in the present situation the year 1921 will close with a higher death-rate for typhoid fever than did 1920.

"From various parts of the country come reports showing that we are right now experiencing numerous local epidemics of typhoid fever. There has been unusual prevalence of the disease in the states of New Jersey, Illinois Pennsylvania, Ohio, New York, North Carolina, Maryland, Georgia, Indiana, Alabama, Kentucky, and Kansas.

"The facts for the last few months indicate that there has been a slackening in the control of this disease. This does not necessarily mean that we shall go back to the periods of high typhoid fever death-rates. With our present-day knowledge of the causes and means of control of typhoid fever we shall probably never again suffer from the high rates of ten years ago. Nevertheless, the check in the decline of the death-rate is a source of great disappointment and suggests further inquiry as to what is at the bottom of the change. Is it necessary in certain states and cities for the health departments to tighten up their control of the sources of distribution of their milk supplies? Has there been any let-down in the sanitation and supervision of water supplies? Are the precautions against carriers as rigidly carried out as they have been in the past? Is the good effect of war-time inoculation wearing off? Is the distribution of antityphoid literature as general or as effective as heretofore? Are markets and other places where food is handled inspected with as much care as formerly?

"These are some of the questions which health officers and sanitarians must ask in view of the recent increase in the typhoid fever death-rate. We have with good reason begun to look upon typhoid fever as a vanishing disease. It is obvious that there is still much work to be done unless we are willing to continue in the unsatisfactory condition of either a stationary or a rising death-rate from typhoid fever."

The method and length of time required to produce a satisfactory artificial immunity is a matter of prime mportance and possibly one of the real objections to this method treatment. Time

does not permit a lengthy discussion of this subject here, but a few fundamental facts will be stated. Since the pioneer work of Wright,[32] Pfeiffer and Kolle,[33] and Russell[34] there has been a constant discussion as to the relative value of vaccination with killed cultures, live cultures and sensitized organisms, and also as to the number and size of the dose and the time interval. It has been used on a large scale in the recent war on large bodies of men under control, and the results have been most excellent in all of them, although the methods differed. The British and American armies used killed cultures in a triple vaccine, containing a single strain each of the Bacillus typhosus, paratyphosus A and paratyphosus B, thus constituting a monovalent vaccine. The British used two doses and the Americans three doses at weekly intervals. The French army used a similar vaccine, except that at the direction of Vincent it was made polyvalent, that is, it contained ten strains of the Bacillus typhosus and single strains of the other two organisms. Vincent recommended the use of four doses at weekly intervals, but due to the exigencies of war reduced it to two. The efficacy of the killed culture vaccine as produced at the U. S. Army Medical School and used with remarkable success in millions of individuals during the past few years cannot be questioned. Similar ones are prepared by various boards of health and also commercially. They usually contain 1000 million Bacillus typhosus, 750 million Bacillus paratyphosus A and 750 million paratyphosus B per cc. The dosage is usually 0.5 cc, followed at weekly intervals by 1 cc, three doses in all. By the end of the first week after the last injection the agglutination titer frequently has reached $\frac{1}{1000}$ or $\frac{1}{2000}$, and in ten days it is frequently $\frac{1}{5000}$ or better. However, the time required to obtain a satisfactory antibody content in the blood is, at the minimum, about three weeks. To be of service in the suggested method of treatment this period of immunization must be shortened.

Gay[35] has been able to obtain very satisfactory immunity by giving the doses on alternate days instead of alte nate weeks, and believes it could be accomplished by a single dose containing the same number of organisms as the three. It is possible, however, that such a dose might be overwhelming. The crux of the situation may be well defined by quoting Vincent and Muratet.[36]

"What is the quantity of vaccine needed to confer immunity and what is the duration of this immunity? As a matter of fact the immunity and its duration are in direct relation not to the number of the injections, nor even, properly speaking, to the quantity of vaccine injected, but to the number of typhoid bacilli injected."

Vincent further believes that the minimum protecting dose of antigen is between 1300 and 2000 million bacilli. Therefore it is proposed to use, for the purpose of producing a rapid artificial

immunity, the vaccine of the U. S. Army Medical School, or a similar one, in three doses of 0.5 cc, 1 cc and 1 cc on alternate days.

Comment. Two cases of typhoid fever of the hypertoxic type are presented. Both were treated with recently artificially immunized blood, and the result in each case has been unusually gratifying. It is not presumed to draw any definite conclusions from two cases. However, a few possibilities suggest themselves.

1. This is not intended as a general treatment for typhoid fever. The mild and moderately severe cases will respond to careful nursing and a high caloric diet.

2. The rationale of this treatment is founded on experimental and clinical facts as they pertain to typhoid immunization.

3. Parenthetically, transfusion for hemorrhage in typhoid fever is justifiable and is the treatment of choice.

4. In this age the opportunity will come to no one man to apply this form of treatment to a large series of cases. It is to be hoped, therefore, that it will be used in the isolated cases and the cases recorded. In this way only will its ultimate usefulness be established.

5. Perhaps it is too much to hope that this may mark the beginning of another epoch in the conquest of this disease and that the annual toll of ten thousand lives in the United States may be reduced to that many hundred.

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CONGENITAL ABSENCE OF THE SPLEEN.

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(From the Babies' Hospital.)

OF all the anomalies relating to the viscera, congenital absence of the spleen is one of the rarest. It occurs as a single abnormality, but more frequently is associated with one or more congenital malformations. In all the reported cases it was an accidental discovery at autopsy. Some of the cases occurred in infants while others were in adults who at no time had discoverable symptoms referable to the absence of an important viscus.

CASE REPORT. Andre P., aged three months, of French parentage, was first seen by one of us on November 15, 1921, and on that

day was referred to the Babies' Hospital for admission, where he was under observation for nineteen days.

The patient was the third of three children. The others were apparently normal in every respect. The child was born at full term after normal delivery and the birth weight was recorded as nine pounds. The infant had not been nursed at any time. He had been fed on mixtures of whole milk, water and milk-sugar with small amounts of wheat flour. The stools had been normal; there had been no vomiting, but the child did not thrive. Prior to the onset of the symptoms, which were the cause of his admission to the hospital, the weight had been recorded as nine pounds.

The symptoms noted by the parents had been "cold in the head" associated with fever as high as 103° F. for one week, and rapid respiration, which was first noted the day prior to admission to the hospital.

Physical Examination. On examination the infant was found to be moderately well nourished and well developed. He looked acutely ill but was not greatly prostrated. Some dyspnea was evident and the skin of the entire body was slightly cyanotic. The weight was 3700 grams.

The measurements were: Head, 14 inches circumference; chest, 13 inches circumference; abdomen, 11 inches circumference; length, 22½ inches circumference. Distance from top of cranium to umbilicus, 12 inches; distance from the umbilicus to the sole of foot, 10½ inches; the anterior fontanelle measured 2 x 2 inches.

The posterior fontanelle was closed. The pupils reacted to light. The ears were normal and the right ear was slightly larger than the left. The lips were of a darker hue than the rest of the body. The throat was normal. The superficial lymph glands were not enlarged. The chest was of normal contour; the respiratory movements were somewhat limited and there were well-marked supra- and infraclavicular retraction. The maximum cardiac impulse was just below the xiphoid cartilage. The right border of the heart, as determined by percussion, was one inch to the right of the midsternal line and the left border two inches to the left of the same line. There was a distinct cardiac murmur heard over the entire precordium and also over the right chest posteriorly. It was systolic in time and transmitted to the vessels of the neck.

The lungs were apparently normal except for the presence of a few scattered moist rales heard at the bases behind. The abdomen was soft and slightly distended. There was a large mass, apparently liver, which occupied the upper quarter of the abdominal cavity. To the right of the midline the lower edge of this mass was horizontal and could be felt about one inch below the costal margin. To the left of the midline the lower edge ran obliquely downward and to the left, disappearing in the flank, where it was felt about two

inches below the free border of the ribs. The reflexes were normal. A left-sided hydrocele of the cord was present.

Clinical Course. During the infant's period of observation in the hospital fever was constantly present, fluctuating between 100° and 102°. For the first ten days he maintained his admission weight of 3700 grams and from then on steadily lost. His weight on the day of discharge was 3500 grams. The stools were normal for the first ten days of hospital observation. During the balance of the period they became more frequent, generally four or five in twenty-four hours. On the seventeenth day both ear-drums were incised and pus obtained.

A routine throat culture was done. This showed no Klebs-Loeffler bacilli. Both the von Pirquet test and the intracutaneous tuberculin test were negative. The urine was straw-colored, clear, acid, contained considerable albumin, a few white blood cells and many hyaline and granular casts. There was no sugar or acetone present. In a second urine examination, a few days later, albumin was present in the same proportion as previously reported, but no casts. One blood examination was done four days after admission. The hemoglobin was 100 per cent. White blood cells numbered 33,300, and were differentiated as follows: Polymorphonuclears, 66 per cent; eosinophiles, 3 per cent; small lymphocytes, 20 per cent; large lymphocytes, 5 per cent; large mononuclears and transitionals, 6 per cent. The platelets were increased in number.

Two roentgenographic examinations were made of the trunk. Both of these showed a cardiac shadow which extended considerably beyond the normal, both to the right and to the left. The liver shadow approximated the findings outlined by palpation as noted above, which proved at autopsy to be a transposition of the right and left lobes.

The infant was removed from the hospital nineteen days after admission; two days later severe respiratory symptoms developed, and he died at home the following day, December 6, 1921.

The autopsy was performed at the Babies' Hospital by the hospital pathologist, Dr. Martha Wollstein. The findings were as follows:

Anatomic Diagnosis: 1. Congenital absence of the spleen.

2. Congenital malformation of the heart (open auricular and ventricular septa—transposition of veins).

3. Congenital malformation of the lungs (supernumerary lobes).

4. Atelectasis and bronchopneumonia.

5. Congenital malformation of the liver (transposition of right and left lobes).

The body was that of a well-developed and fairly well-nourished white male infant. No skin lesions were present.

Lungs. No pleurisy. Left lung had three lobes divided by two well-marked fissures. It was well aërated throughout. The right lung had four lobes, *i. e.*, in addition to the three normal lobes there was a triangular lobe separated from the lower lobe by a well-marked fissure and corresponding to the sublingual lobe in the dog. In addition the right lower lobe had a small fissure near its upper angle extending about 3 cm., so that there was an incomplete fifth lobe. The right lower lobe was blue in color, smaller than the left lower, partly atelectatic and partly, in its anterior portion, the seat of a bronchopneumonia.

Bronchial Lymph Nodes. Normal.

Heart. Normal in position, pointing to the left and larger than normal. At the base it measured 5 cm. in diameter. In length it measured 6 cm. The apex was very round, and there was a shoulder to the right ventricle, which made the base wider than normal. The auricular appendages were much rounded. Both auricles were distended with softly clotted blood, making the appendages seem longer than usual. The ventricles were of about the same size and thickness. The pulmonary artery and aorta were normal. The ductus arteriosus was closed. The foramen ovale was very widely open. The interventricular septum had a large opening, 1.5 cm. in diameter, in its upper third. The venæ cavæ emptied into the left auricle and the pulmonary veins into the right auricle. The valves were all normal.

Liver. The liver measured 14 cm. transversely. The larger lobe was on the left side and its anteroposterior diameter was 8 cm. The smaller right lobe measured 6.5 cm. anteroposteriorly. The suspensory ligament and the inferior fissure were to the right of the gall-bladder, which was in the left lobe. The other lobes of the liver were normal. On section the liver substance was congested, but otherwise normal.

Spleen. Completely absent. No supernumerary spleens found after prolonged search. The celiac axis had been removed, so that search for the splenic vessel could not be made.

Kidneys. Lobulated and on section congested, with markings blurred. Cortex was not thickened.

Suprarenals and Pancreas. Normal.

Stomach and Intestines. Normal throughout. The cecum was in its normal position on the right side. The appendix was normal. Cecum and mesocolon were very freely movable.

Smears from the heart's blood were taken at autopsy and stained with Wilson's stain. They showed no abnormal forms of cells. The polynuclear leukocytosis noted during life was evidently due to the bronchopneumonia present, and there was nothing in the blood morphology to indicate any abnormality of the lymphatic system.

Discussion. In the most recent publication regarding the spleen, Sir Berkeley Moynihan states the following: "The spleen is not always present in man, though its absence is excessively rare. Its occasional absence is noted in animals. In the vertebral kingdom its position is not constant. In the majority of animals it is outside but associated with the gastric segment; but there are instances of its development in connection with the lower end of the canal and others where it is scattered." In many of the text-books of pathology and pathologic anatomy, such as Aschoff, Ribbert, Ziegler and Delafield and Prudden, it is stated that cases of complete absence of the spleen have been known to occur. In the *American Text-book of Pathology* the following statement regarding this condition is made: "Complete absence of the spleen is rare. In these cases the organ is usually represented by several small scattered masses of splenic tissue (splenunculi) which, on account of their size and location, are in danger of being overlooked." Kaufman also noted that "Absence of the spleen occurs but seldom," and he adds the interesting comment that the disappearance might occur in fetal life from an embolus of the splenic artery. Adami and Nichols observe that complete absence of the spleen is the rarest of the congenital anomalies affecting the spleen and that it is frequently found associated with other grave defects of development. "About thirteen cases are on record, but only one, that of Birch-Hirschfeld, is beyond cavil. More often the place of the spleen is taken by scattered nodules of splenic tissue in various parts (splenunculi)."

They refer to Albrecht's case, in which there were nearly four hundred of these splenunculi scattered throughout the abdominal cavity. This condition was present in a twenty-six-year-old man who died of nephritis. The normal splenic organ was wanting in this individual, and these accessory spleens varied greatly in size, the smallest being only as large as the head of a pin. In the case of congenital absence of the spleen reported by Sternburg the patient was a woman, aged seventy-three years, who had had four normal pregnancies and had had "lung trouble" for a long period of years. She died shortly after admission to the hospital, and at autopsy it was discovered she had advanced pulmonary tuberculosis. There was no spleen found nor any accessory spleens. The retroperitoneal lymphatics were not enlarged. The branch of the celiac artery, which should have corresponded to the splenic artery, was broken up into a series of small twigs, which passed in part to the stomach and in part to the colon. Sternburg quotes an article by Toldt, which we have not been able to locate, in which 17 cases had been collected, and of these only 4 were unassociated with other abnormalities. In the other 13 there were abnormalities of different grades; 11 of the cases were in the newborn or in infants in the first weeks of

life and 6 were among adults. These adults varied in age from eighteen to forty-nine years of age and in only 3 of these was the absence of the spleen the only abnormality found. Birch-Hirschfeld's case was noted in an infant who died directly after birth. The infant was well nourished and well developed, but the liver was very large. The spleen and the splenic vein were absent but the portal vein was normal.

In 1871, when this report was presented by Birch-Hirschfeld, he stated that he could find no other cases in the literature except one,* which was not accessible.

Glinski reported a case of a woman, aged forty-five years, who died of pulmonary tuberculosis. There were no other abnormalities noted at autopsy, no lymphatic hypertrophy, nor hypertrophy of other organs. Riches reported a case of a woman, aged forty-five years, who died in an institute for the insane following an operation for a round-cell sarcoma. He noted that this neoplasm occupied the site of the omentum; there were secondary deposits in the mesentery and lymphatic glands in the immediate vicinity of the growth. The autopsy findings failed to reveal any congenital abnormalities and careful search failed to reveal the presence of the spleen. Rose's case from Georgetown, British Guinea, occurred in a negro, aged fifty-six years, who died following an operation for strangulated hernia. At autopsy no spleen was found nor was there any splenic artery. He mentions the fact that there were no splenunculi present.

Hodenpyl's case, which he termed "apparent absence of the spleen," occurred in a negro, aged thirty-two years, who died after an illness of a week's duration. A compensating hyperplasia of the mesenteric and retroperitoneal lymph glands was present as well as a lymphatic hyperplasia of the suprarenals, the intestines and a cellular proliferation of Glisson's capsule.

The case reported by Martin in 1826 was in an infant, aged eight and a half months, who died following a series of convulsions. There was no spleen found at autopsy. The stomach was on the right side; above, it touched the liver and the diaphragm. The greater curvature touched the right kidney and the lesser touched the vertebral column, the head of the pancreas and the abdominal aorta. The first part of the duodenum was on the left side but the rest of the intestine was normal. The liver occupied both hypochondriac regions and was divided into two parts of equal size. The heart was large and the pulmonary artery and aorta were transposed. The auricles were large and communicated with each other. Each auricle furnished a superior and inferior vena cava. There was a single ventricular cavity, and, as Martin states, the heart resembled the heart of a fish.

* Pohl, Lips, 1740, De Defectu Lienis.

Koch and Wachmuth's case occurred in a well-nourished and well-developed tinsmith, aged forty-nine years, who died of bronchopneumonia. At the autopsy the diagnosis was confirmed; all the organs were anatomically normal, but the spleen and splenic artery were absent. The case reported by Lebby in 1834 could hardly be classified as congenital absence of the spleen. This report concerned an adult negro (age not mentioned) who was executed and the body autopsied for the instruction of medical students. The negro was sixty-eight inches tall, badly nourished but well developed. He gave a past history of "bilious intermittent and remittent fevers." The author states that the spleen was absent, but relates further that "Contiguous to the pancreas was a sac the size of a large orange, oblong in form, of a dark ash color, shrivelled in appearance and imparting to the hand the sensation of squeezing a decayed orange; upon opening the sac it was found to contain pus of a creamy hue and consistency."

Ramsey's case also occurred in a negro slave, aged twenty-eight years, who had been ill for almost a year with intestinal symptoms accompanied by great loss of weight. At autopsy no spleen was found. As the author expressed it, "The spleen was wanting *in toto*, there was some suppurative matter about its situation, but nothing remained of it except a few ligamentous traces to mark the place of its existence." From this description one is obviously not justified in terming this case one of congenital absence of the spleen.

In an editorial notice in 1845, J. J. Sachs refers to a case reported before a Russian medical society the previous year by a Dr. Meinhard, of a woman, aged forty-seven years, who died in Peter-Paul's Hospital, in whom no trace of a spleen nor of splenic bloodvessels could be found at autopsy. There has evidently been some confusion in the literature regarding this case and the various references to it. Jelenski refers to this case and gives the age of the woman as fifty-seven years. Hodenpyl refers to the citation of Jelenski's and states that the latter mentions that Sachs performed an autopsy on an adult who had no trace of a spleen. As a matter of fact there was only one case, which was the one autopsied by Meinhard. Sachs merely referred to this case in an editorial note which was quoted by Jelenski thirty-five years later, and has since often mentioned as his own case.

Olaechea's case, with a carefully recorded autopsy, occurred in a young man who died of "tifomalaria." The age of the patient was not mentioned, but as he was a sergeant in a Peruvian regiment it may be assumed that he was a young man. At autopsy no trace of a spleen was found nor was there any evidence of suppurative splenitis. Fatty and connective tissue occupied the normal site of the spleen. There were no anomalies of the other organs, nor was there any scar of the abdominal walls through

which the spleen might have been previously removed. The liver was congested and there was a congestion of Peyer's patches, but no ulceration. The bronchial and mesenteric lymph nodes were greatly enlarged, some of the latter being 2½ cm. in diameter. The inguinal and axillary lymph nodes were also greatly enlarged. The lymphatic hypertrophy was believed by the author to have been compensatory, due to the absence of the spleen.

Hodenpyl refers to a case cited as absence of the spleen reported by E. Moroni, but was unable to obtain access to the publication. We were able to secure this publication and discovered that it related to a dog whose spleen had been extirpated and who had been observed for a period of a year after splenectomy.

Kohlhaas has recently reported a case of a woman, aged fifty-four years, who died of cerebral hemorrhage due to arteriosclerosis. All the viscera were normally situated, but no spleen was demonstrable; careful search for accessory spleens or enlarged lymph glands was unsuccessful. There was no hyperplasia of the lymphoid tissue of the intestine. The liver was small and the splenic artery came well developed from the tripus Halleri. The bone-marrow was chiefly of a reddish color and a small portion was yellowish. Microscopic findings were normal. At the greater curvature of the stomach and at the diaphragm a collection of fat was found in the splenic region about 5 cm. long, 2 cm. wide and 1 cm. thick; on cross-section this was found to contain a small lymph gland 1 cm. long and 0.02 cm. thick; microscopically this showed no deviation from the normal lymph gland.

Robert's case occurred in a female infant who was extremely well developed except for a rudimentary forearm, wrist and hand. The infant died three days after birth. The autopsy showed an arrested development of the stomach and absence of the spleen and omentum. The stomach had failed to undergo a primary dilatation, but retained a configuration resembling that of the duodenum.

Arnold's case occurred in a female infant who died at the age of fifteen weeks. The autopsy showed anomalies of the heart and large cardiac bloodvessels; anomalies of the pulmonary veins; anomalies of the portal vein and the ductus venosus Arantii; anomalies of both venæ cavæ and of the hepatic veins. The spleen was missing. No changes were demonstrable.

Heusinger has collected 2 cases which are solely of historical interest. The first was reported by Lemery* of a female infant who died at the age of eight days. Externally she was apparently normal, but at autopsy it was discovered that the entire intestinal canal was absent as well as the spleen and the liver. Occupying the normal site of these organs was a "fleshy mass as large as a

* Mémoirs de l'Académie des Sciences, 1704, p. 21.

child's head connected with the stomach but not with the anus, which contained arteries and veins." The second case dates back to the 16th century† and is reported as follows: "In September, 1564, a famous Antwerp merchant named Matthias Oetchius, a native of Germany, died and came to autopsy on the next following day. It was specially desired to ascertain the condition of the digestive organs, particularly the liver and spleen, for he had suffered some years previously from dropsy, a disease which is always connected with a primary or secondary pathologic condition of the liver. The expert surgeons searched under the diaphragm and the false ribs, but were unable to find any trace of these organs. This is a remarkable and unheard-of-case, for the substance of the entire canal was fleshy, much firmer than muscle tissue, so as to equal nearly the firmness of heart muscle."

The case herein presented, as well as the other true cases of congenital absence of the spleen included in our collection, may be of some value in determining the importance of this organ. Although this congenital abnormality is often associated with other anatomic defects of development, it does occur as a single defect. In 9 of the cases from our collection the individuals with this anomaly reached middle life without recognizable disturbance, and one woman, who had had four normal pregnancies, died at the age of seventy-three. In our case and in the 4 other infants recorded there was apparently no hyperplasia of lymphoid tissue. In 7 of the adult cases, which were undoubtedly true cases of congenital absence of the spleen, there was no lymphoid hyperplasia, while in 2 there was definite lymphoid hyperplasia which was termed by the writers compensatory. If the lymphoid hyperplasia was in any way related to the absence of the spleen it is difficult to understand why the condition was not present in every case. In view of the fact that it was present in only 2 of the cases in our collection, it would seem that causes other than congenital absence of the spleen might have been responsible. From a review of the literature of this unusual anomaly one is justified in the conclusion that in certain individuals congenital absence of the spleen is apparently not a serious handicap.

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DELAY IN THE TREATMENT OF CANCER.[1]

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Several years ago the statistics on delay in the treatment of cancer as seen in the first surgical or Cornell division of the New York Hospital were investigated. The results were quite startling, to say the least. Our cases were coming so late and frequently in such hopeless condition that a determined effort was made to ascertain the causes of delay.

Over 100 consecutive cases were questioned at length as to the time lost after the initial symptoms, first, before consulting a physician, and second, before entering a hospital for study and treatment. Incidentally we classified the physician's advice as good or poor, accordingly as he urged operation or counseled delay and palliation. We then classified our cases under curable, probably curable, incurable, operable and inoperable headings.

[1] Read before the Society for the Control of Cancer, November 7, 1921.

From these findings, meager though they were, it was at once apparent that patients procrastinate and delay for a considerable time after symptoms develop, that the physician's advice is as frequently wrong as right, that another and longer period of delay ensues before entering hospital, and that our patients finally reach us in such an advanced stage that only palliative or life-prolonging treatment is possible.

These figures, as ascertained after most painstaking investigation, were read before a scientific society in this city and offered to the leading medical journal of the country. Much to our surprise the article was rejected as casting reflection on the profession, and was rather harshly criticized. It was, however, promptly accepted and printed by the leading scientific medical journal of the country. The facts as presented were verified and substantiated by numerous writers before and since that article appeared and the popular medical journal reviewed the article at considerable length with no word of criticism.

Recently a further investigation has been made of approximately 250 additional cases, and the results are too strikingly similar to be very inaccurate. It must be remembered that the facts were obtained by many different men, working in ignorance of any desired goal, and that the tabulations and comparisons have been made by still other men, selected for their special knowledge and training, but not the responsible surgeons in charge. In this way personal bias has been, we hope, to a large degree eliminated. Inaccuracies naturally will creep into such a compilation, but we trust and believe that we have approximated the truth.

Our findings are that a delay of approximately one year occurs in the average case before adequate surgical care is sought. This means a year of delay after the development of symptoms or the appearance of a growth. Unquestionably the growth is always present for some time before symptoms or the tumor appears.

From the surgical standpoint we can state emphatically that nearly all cancers or malignant tumors are curable by the knife or other destructive measures if seen early enough. Unfortunately a considerable proportion of cases occur in deep-seated, inaccessible or non-symptom-giving locations. In such instances it is but natural that we rarely see curable cases. Mistakes in diagnosis here are also readily understood and are forgivable.

From the standpoint of our present knowledge the only hope of increasing our percentage of cures lies in obtaining cases earlier in the disease. We must shorten the time from the patient to the physician and from the physician to the hospital; possibly even we can shorten the time lost before symptoms develop by regular, systematic, complete physical examinations at not too infrequent intervals. This last idea, I fear, is quite utopian at present.

We can and must, however, reach our patients earlier, before the disease has spread beyond possible removal. The physical limits of operative removal have surely been nearly if not quite attained. Progress can come only by shortening the time preceding operation.

Education of both the laity and, I regret to say, the physicians must be pushed to the point where only wilful self-neglect can prevent timely proper treatment and a very high percentage of cures. Cancerphobia or hysteria must be avoided, of course, and grewsome discussions of neglected cases are not usually helpful. In general a calm, rational, thoughtful statement is more effectual than hysterical or alarmist appeals. After all, patients are quite reasonable in their views of health and disease if only given a fair insight into conditions.

Such methods of propaganda have been used repeatedly here and elsewhere on similar subjects, and with marked success. We firmly believe that a like success will follow sincere and earnest work in this field also. Teamwork, persistence, tact and courage will accomplish as much in our cancer work as they have in the antituberculosis campaign and in general hygiene.

Preventive treatment of malignancy offers a very hopeful field for research and practical application. We do not know the cause of cancer, but we do know what underlying conditions favor its implantation and growth. Such conditions are frequently amenable to simple and safe remedies. A trivial operation for the removal of an innocent growth, a small but persisting ulcer, a fissure, an irritated scar, etc., may prevent a severe and mutilating procedure a few years later. Even the adoption of a simple, proper diet, good hygiene and the avoidance of all excesses in eating, drinking, smoking, etc., may well be considered preventive measures against cancer. Delay in the use of the simple remedy is as foolish as in definitely established growths, or more so, as preventive cures are so infinitely safer and more sure than remedial attacks.

Resume of Cases. One hundred and fifty cases gave *time lost* after symptoms developed and before consulting a physician from no time to ten years. Average time, twenty-four weeks.

Time from onset of symptoms to time of consulting physician obtained in 150 cases. One of these, a slow-growing sarcoma of the arm of twenty-five years' duration, is not included in the average. Others range from no time lost to ten years; 79 consulted a physician in one month or less from the onset of symptoms. Average time, twenty-four weeks.

Time from Consulting Physician to Time of Entering Hospital. Obtained in 141 cases. Ranges from no time lost to nine years. With one exception all who waited over one year were cases in which the physician gave wrong advice. This was a woman with carcinoma of the cervix who waited seven years; 68 entered the

hospital within one month from the time of consulting a physician. Of these all but 3 were advised correctly. Average time, twenty-four weeks.

Time from onset of symptoms to time of entering hospital in those cases in which it was not stated when the physician was consulted, 90 cases, excluding those given above. Average time, fifty-five weeks.

PHYSICIAN'S ADVICE:

	Total.	Right.	Wrong.
Number curable	43	32	11
Probably curable	24	13	11
Incurable	83	39	44
Operable	74	51	23
Inoperable	76	33	43

I wish to express my thanks to Dr. Charles L. Gibson for the privilege of publishing these statistics, as all the cases occurred in his service and were operated by him and the other members of the attending staff of the first surgical or Cornell division of the New York Hospital. I wish also to thank Dr. Morris Weeden for assistance in collecting the statistics and tabulating them.

THE VIBRATING SENSATION IN DISEASES OF THE NERVOUS SYSTEM.

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The "vibrating sensation" is the peculiar vibrating or trembling sensation which is felt when the foot of a *large* vibrating tuning-fork is placed firmly in contact with a subcutaneous bony prominence or surface in many parts of the body—the malleoli or the styloid process of the ulna or the sternum for example. The sensation is also sometimes described as bone sensibility or pallesthesia. Attention was specially directed to this sensation by Egger in France in 1899. Many articles have been written on the subject in foreign medical literature and a few in English literature. In previous articles[1] I have pointed out the value of this sensation in diagnosis, and described the method of testing it.

In this article I shall record merely my own results in clinical work, since I first commenced to test the vibrating sensation in the routine examination of the nervous cases seventeen years ago.

A tuning-fork is supplied by Messrs. Woolley & Sons, Victoria Bridge, Manchester, which is very suitable for testing this sen-

[1] British Med. Jour., July 20, 1907: Diseases of the Spinal Cord, London, 1908, (1911), p. 79; Jour. Neurol., August, 1911; Lancet, February 9, 1918.

sation. It is seven and one-half inches long, marked A 440, and has an oval metal foot-piece (long diameter one and one-quarter inch) attached to it. Nearly all my observations were made with this tuning-fork.

A few control observations are desirable, to see if the patient clearly recognizes the nature of the sensation before a routine examination is made.

The vibrating sensation is felt when the foot of the vibrating tuning-fork is placed over the bones of the limbs, and on the nails, on the iliac spines, sacrum, vertebral spines and bones of the thorax. It is particularly well felt over the sternum. In clinical work convenient points for testing are the styloid processes of the ulna, the inner surface of the tibia, the malleoli, the anterior superior iliac spine and the nails of the fingers and big toes. In the normal condition the vibrating sensation is always felt at these points. The sensation is not felt on the bones of the skull, but the vibrations are heard.

Normally the vibrating sensation is also felt when the foot of the vibrating tuning-fork is placed *firmly* in contact with the anterior abdominal wall.

On the anterior abdominal wall, at the level of the umbilicus, the vibrating sensation (tested with the tuning-fork I have described at the commencement of this paper) is distinctly felt in the normal condition. Also it is distinctly felt on the abdomen between the umbilicus and the thorax. On the lower part of the abdomen (below the umbilicus) it is not felt so distinctly; but by *firm* pressure of the tuning-fork the sensation is usually felt.

In 50 consecutive cases (normal individuals, or cases of mild ailments not affecting the nervous system), the vibrating sensation produced by my tuning-fork was felt on the abdomen at all the parts just mentioned, both above and below the umbilicus. But occasionally in very *stout* persons I have found that the vibrating sensation cannot be felt on the abdomen.

Conduction of the Sensation. The nerve fibers conducting the vibrating sensation apparently do not decussate in the spinal cord. In many cases of unilateral lesion of the spinal cord the vibrating sensation has been lost only on the side of the lesion, below the level of the disease; whilst sensation for touch, pain, and temperature have been lost on the side opposite to the lesion.

The vibrating sensation is probably not conducted upwards in the gray matter, since the gray matter has been entirely destroyed in hematomyelia at the seat of the disease, and yet the vibrating sensation has been unaffected though the sensations for pain and temperature were markedly affected. (Bing)

In one of my cases of syringomyelia (of twenty years' duration) the vibrating sensation was normal though sensation for pain and temperature were lost on the hands and arms, and the hand muscles markedly atrophied.

Bing considers it probable that the vibrating sensation is conducted upwards in the posterior columns of the white matter of the cord.

In a considerable number of cases of spinal disease, which from their symptoms have been apparently cases of combined posterolateral degeneration, I have found the vibrating sensation lost and muscular sense impaired at an early period of the disease, while other forms of sensation have been normal at this period.

General Remarks on the Value of the Vibrating Sensation in Diagnosis.

1. Loss of the vibrating sensation may be a useful indication of *organic affection of the nervous system* at the earliest stage of the disease, when symptoms and signs of such lesions are very few and slight—as at the earliest stage of peripheral neuritis, tabes, and posterolateral sclerosis. Sometimes in such cases, at the earliest stages, we may detect only one or two symptoms or signs in favor of *organic* nervous disease, and if we find the vibrating sensation lost, then this is an additional indication confirming our suspicions of commencing lesion of the nervous system.

2. Loss of the vibrating sensation is frequently one of the *first indications* of *sensory* affection in many lesions of the spinal cord and in peripheral *multiple* neuritis. In such cases the vibrating sensation is often lost before other forms of sensation are affected. At a later date anesthesia to tactile and painful sensations and to temperature may occur.

3. The vibrating tuning-fork is a very delicate *test for sensation:* and if we have found the sensation normal to touch, pain, temperature, etc., before concluding that sensation is entirely unaffected, it is desirable to test the vibrating sensation; since we may, as just mentioned, find it lost though otherwise sensation is normal.

4. When *partial recovery* occurs in cases of spinal lesions which have caused marked anesthesia the vibrating sensation may remain markedly affected though other forms of anesthesia have disappeared. Thus in a case of shrapnel wound of the spine, followed by complete paraplegia and anesthesia, with bladder symptoms, after laminectomy marked improvement followed. Two years later the patient was able to walk though the legs were spastic; the bladder symptoms had disappeared and sensations of touch, pain and temperature were felt distinctly; but the vibrating sensation was still lost on the legs.

In hemianesthesia from cerebral lesions we find that when recovery occurs the vibrating sensation returns *before* tactile sensation. Thus in a case of hemiplegia and hemianesthesia of sudden onset (probably due to hemorrhage), at first sensation, to the vibrating

tuning-fork and to all forms of sensibility was lost on the left side. At a later date, when marked improvement had occurred, the vibrating sensation and also painful sensations were felt on the left side; but sensation to touch was lost. This is thus the opposite of the condition in many cases of spinal anesthesia.

In spinal anesthesia the vibrating sensation is often the first to be affected and the last to recover; while in cerebral anesthesia the vibrating sensation may be the least affected, and if affected it may recover before tactile anesthesia. I have never met with a case of loss of the vibrating sensation alone in a cerebral lesion.

5. Certain diseases of the spinal cord affect only the motor parts of the cord. Anesthesia to any form of sensation would therefore exclude such diseases, or at least show that the pathologic changes had spread to the parts of the cord in which sensory structures are situated. Hence the detection of any affection of sensation is of great diagnostic value. But at first sensation to touch, pain and temperature may be normal; and until we test the vibrating sensation we may consider that the disease is localized entirely in motor parts. If, however, we find that the vibrating sensation is lost we have then an indication that the disease has affected sensory parts of the nervous system; and we can therefore exclude at once all diseases which are known to affect only motor parts of the nervous system. Thus in cases which we suspect to be anterior poliomyelitis or amyotrophic lateral sclerosis, we may exclude these diseases if we find the vibrating sensation lost.

6. The vibrating sensation is also sometimes of service in the diagnosis between paraplegia due to organic disease and paraplegia due to hysteria, functional affections or malingering. In any case of paralysis of the legs, if we find that the vibrating sensation is lost, while other forms of sensation are felt, and the patient persists in this statement in spite of suggestions to the contrary, then I think that hysteria or functional affection is very improbable. In paraplegia due to hysteria or functional affection or malingering my experience has been that if the vibrating sensation is lost other forms of sensation will also be affected, or that by suggestion, through the form of the question, the patients will state that they are affected.

7. The loss of the vibrating sensation on the abdomen may be of service in indicating the upper limit of a spinal lesion in traumatic and other spinal affections when other forms of sensation are not affected. Thus the vibrating sensation may be lost on the abdomen up to one inch above the umbilicus, while it may be felt on the abdomen above this level. This would be a guide to the level of the spinal lesion. (In testing, the foot of the tuning-fork should be pressed very firmly against the abdominal wall.)

The Diagnostic Value of Loss of the Vibrating Sensation in Various Nervous Diseases.

In certain diseases of the nervous system affecting motor structure only the vibrating sensation is always felt. Thus I have never found it lost, even at an advanced stage of the disease, in cases of amyotrophic lateral sclerosis, primary lateral sclerosis, progressive muscular atrophy, acute and chronic anterior poliomyelitis (in the infant or adult) and paralysis agitans. Also I have never found it lost in pseudohypertrophic paralysis, idiopathic muscular atrophy, neurasthenia (unassociated with hysteria). Loss of the vibrating sensation would therefore be a strong point against the diagnosis of the affection just named.

The following remarks will indicate the value of the vibrating sensation in the differential diagnosis of various diseases.

At the earliest stage of *mutiple peripheral neuritis*, from various causes, loss of the vibrating sensation may often be detected before loss of any other form of sensation. At this earliest period often the chief symptoms are pains in the legs and muscular tenderness, and it is often difficult to decide if these are due to commencing *organic* disease or not. On examination at this earliest period no anesthesia to tactile impressions, pain or temperature may be detected, and though the patient may complain of weakness in the legs, no definite paralysis or paresis may be detected. Also the knee-jerks may, at this *earliest* period, be still obtained. But in these cases two symptoms may be frequently detected which clearly indicate commencing organic disease; these are loss of the tendo-Achillis reflexes and loss of the vibrating sensation. At a later period in these cases the knee-jerks disappear and muscular paralysis and loss of other forms of sensation may be detected. We have thus four very early signs of *multiple* peripheral neuritis: (1) Pain in the legs; (2) tenderness of the muscles; (3) loss of the tendo-Achillis jerks; (4) loss of the vibrating sensation.

These remarks apply to alcoholic neuritis, arsenic neuritis, diabetic neuritis and multiple neuritis of other forms.

Nervous Complications in Diabetes Mellitus. In diabetes pains in the legs and tenderness of the calf muscles are not infrequent symptoms and are usually attributed to slight diabetic multiple peripheral neuritis, but paresis or paralysis is very rare. In these diabetic cases we often find that the tendo-Achillis reflexes are lost, and less frequently the knee-jerks also, and that the vibrating sensation is lost, though other forms of sensation are felt. In these very early cases of nervous complications, at first, only one of these symptoms may be present. Thus pain may be the only nervous symptom or loss of the tendo-Achillis reflexes or loss of the vibrating sensation, while later all these three symp-

toms may be present and additional symptoms may develop. I have found occasionally, in diabetic patients, that the vibrating sensation has been lost on the legs, even when the knee-jerks and tendo-Achillis reflexes have been present and the patient has not suffered from pain in the legs except cramp in the calf muscles at night. In other early cases and much more frequently, two of the symptoms just named have been present—pain and loss of the vibrating sensation or loss of the vibrating sensation and loss of the tendo-Achillis reflex or pain and loss of the tendo-Achillis reflex. Hence we may say that in diabetes mellitus the vibrating sensation is occasionally lost on the legs (malleoli and inner surface of the tibia) when other nervous symptoms are absent or slight. But the additional early symptoms just mentioned usually develop soon and others may develop later.

In 100 consecutive cases of diabetes I found the vibrating sensation was lost on the legs (malleoli and inner surface of the tibia) in 18 cases.

In a few of the cases of diabetes presenting these nervous symptoms usually described as "neuritis," pathologic examination has revealed changes in the peripheral nerves, but not always. I have found (in a case which I have recorded) that the peripheral nerves showed no definite microscopic changes (in the fibers examined); the posterior nerve roots, however, showed marked degeneration at their entrance into the cord directly after passing through the pia mater.

Loss of the vibrating sensation is often a useful sign in the differential diagnosis of multiple peripheral neuritis from acute anterior poliomyelitis affecting both legs, since in the later affection the vibrating sensation is not lost.

The symptom was of particular service in a case which I saw at the end of the war period. A man had been invalided home from France; paralysis of the legs had developed and slight paresis of the arms. The knee-jerks and tendo-Achillis reflexes were lost; the bladder was unaffected. Sensation to touch, pain and temperature could be felt. A diagnosis of spinal-cord affection and a very unfavorable prognosis had been given previously. On examination anterior poliomyelitis appeared very probably, as pain and muscular tenderness in the limbs had not been prominent symptoms, though both were present. But three symptoms were against the diagnosis of anterior poliomyelitis (subacute or acute):

(1) The vibrating sensation was lost on the legs; (2) the paralysis in the arms was more similar in its distribution to that of peripheral neuritis than to anterior poliomyelitis; (3) The intercostals were not paralyzed, though both arms and legs were affected.

Chiefly on account of the loss of the vibrating sensation I gave a diagnosis of multiple peripheral neuritis and a favorable prognosis. In the course of many months complete recovery occurred.

In *sciatica* and in *primary brachial neuritis* I have never detected loss of the vibrating sensation.

In lesions of a *single peripheral nerve* or a *peripheral nerve trunk* I have never found the vibrating sensation lost, when tested with the tuning-fork I have described in this article, even though other forms of sensation (to touch, pain or temperature) have been affected. Occasionally I have found the vibrating sensation much diminished but never lost, and in most cases it is felt quite well. This is a point sometimes of service in differential diagnosis. In a case of localized paralysis (whether other forms of sensation are lost or recognized), if the vibrating sensation is *completely* lost a lesion of a *single* peripheral nerve or nerve trunk can be excluded as the cause of the paralysis.

In *acute anterior poliomyelitis* of the infant and adult the vibrating sensation is unaffected. This fact is occasionally of much service, as already mentioned, in the diagnosis between multiple peripheral neuritis and acute anterior poliomyelitis causing paralysis of both legs. Usually the pain and muscular hyperalgesia in peripheral neuritis is so pronounced that the diagnosis is easy, but we have to bear in mind that occasionally in acute anterior poliomyelitis at first some pain and muscular tenderness may occur, and occasionally in peripheral neuritis these two symptoms are not very pronounced at first. The loss of the vibrating sensation would be in favor of multiple peripheral neuritis and would show that sensory structures in the nervous system were affected, and that the case was not one of acute anterior poliomyelitis.

In the diagnosis between acute anterior poliomyelitis and *acute disseminated myelitis* or *acute myelitis* the vibrating sensation is helpful. All three diseases may cause paralysis of both legs, and at first sensation to touch, pain and temperature may be normal in acute disseminated myelitis or acute myelitis, as well as in acute anterior poliomyelitis, but in the two former affections the vibrating sensation is often lost. The vibrating sensation may then be of much service in the diagnosis; if lost, acute anterior poliomyelitis may be excluded.

I have found the vibrating sensation of much service in the diagnosis of acute anterior poliomyelitis from the two affections just named and from other spinal diseases, and have recorded cases.

In chronic (and subacute) anterior poliomyelitis the vibrating sensation is not lost, and this fact is occasionally of service in the differential diagnosis of these affections from multiple peripheral neuritis and other spinal cord diseases. Thus in two of my cases of slowly developing paralysis of the legs, with loss of the tendo-Achillis reflexes, the fact that even the vibrating sensation was unaffected (as well as other forms of sensation) was a point, along with others, in favor of chronic anterior poliomyelitis, and enabled

one to exclude many other diseases which might have produced similar motor symptoms.

Primary *lateral sclerosis* is certainly an *extremely rare* disease and can be excluded in any cases in which the vibrating sensation is lost. In all cases which appear to be instances of this rare affection the vibrating sensation should be tested before the diagnosis is given. In one of my cases of spastic paraplegia the fact that the vibrating sensation was present at the end of twenty years was one point, along with others, in favor of the diagnosis of primary lateral sclerosis. (In this case the bladder and rectum had not been affected, no wasting of hand muscles had developed, sensation was unaffected and no signs could be detected of affection of any part of the spinal cord except the lateral pyramidal tracts even at the end of twenty years.) In another case of spastic paraplegia of fifteen years' duration loss of the vibrating sensation, slight nystagmus and occasional diplopia were points against primary lateral sclerosis and in favor of disseminated sclerosis.

In *amyotrophic lateral sclerosis* the vibrating sensation is not lost even at the terminal stage of the disease. In any case of suspected amyotrophic lateral sclerosis, loss of the vibrating sensation would be evidence against this diagnosis.

In many cases which have presented the symptoms of *combined posterolateral spinal degeneration or sclerosis* (*ataxic paraplegia*) I have found the vibrating sensation lost at a very early stage of the disease. At first the symptoms have been chiefly slightly impaired coördination (slight ataxia), Babinski reflexes, impaired muscular power and loss of the vibrating sensation, while other forms of sensation have been felt. Later ankle-clonus and spastic condition of the legs have developed. In some of these cases at a later period sensation to touch, pain and temperature have been much affected. At the earliest stage the loss of the vibrating sensation is a valuable sign of commencing organic disease and is often of much service in diagnosing these cases from functional affections or malingering. I have recorded such cases elsewhere. I may mention one, however, which was of special interest:

A man consulted me in January, 1917, complaining of weakness and heaviness in the legs and slight unsteadiness in walking. He was called up for military service and considered that he was unsuitable on account of these symptoms. The question of malingering or neurasthenia had to be considered. I examined him very carefully, but could then detect no signs of organic disease. He was able to walk alone and showed only very slight unsteadiness, but complained that his legs felt heavy and weak.

In May, 1917, I again examined him and then detected (1) that the gait was slightly ataxic; (2) that the vibrating sensation was lost on the legs, but other forms of sensation were unaffected; (3) that the plantar reflexes were difficult to obtain, but several

times a Babinski reflex was obtained. No other signs of organic disease could be detected, but from the symptoms just named I gave a diagnosis of commencing spinal disease.

In November, 1917, I again examined him. Then the chief symptoms were: (1) definite paresis of the legs; (2) ataxic gait; (3) slight spastic condition of the legs; (4) knee-jerks increased and ankle-clonus and Babinski reflex on each side; (5) muscular sense greatly impaired; (6) vibrating sensation lost on both legs but other forms of sensation recognized. At this period there was no doubt as to the diagnosis of organic spinal disease, and posterolateral sclerosis or degeneration was very probable; but at the earlier examination in May the only definite indications of organic disease were the loss of the vibrating sensation and the occasional Babinski reflex.

I have had many spinal cases in which at first the chief symptoms have been: (1) loss of the vibrating sensation while other forms of sensation have been normal; (2) slight incoördination in walking or affection of the muscular sense in the legs, and (3) Babinski plantar reflexes. These cases have usually developed later marked symptoms of posterolateral degeneration (or sclerosis) ataxic paraplegia.

In *disseminated sclerosis* sensation is very often reported as normal, and this is probably correct as regards sensation for touch, pain and temperature; in other cases these sensations are definitely affected. But if the vibrating sensation be tested it will be found to be lost in a large number of cases of disseminated sclerosis, though other forms of sensation are felt distinctly.

In many cases of disseminated sclerosis I have found the vibrating sensation lost on the legs; in some cases lost on the lower half of the abdomen and also on the legs; in others on the whole of the abdomen and the legs. In a few cases the vibrating sensation has been lost on the middle or lower part of the abdomen but not on the legs and chest. In one case the vibrating sensation was lost only on one-half of the lower two-thirds of the abdomen.

The abdominal and epigastric reflexes are usually lost when the vibrating sensation is not felt on the abdomen in disseminated sclerosis.

In atypic cases of disseminated sclerosis, when the symptoms are chiefly those of spastic paraplegia, the case may closely simulate primary lateral sclerosis. But if we find that the vibrating sensation is lost this symptom would exclude primary lateral sclerosis and would be one point in favor of disseminated sclerosis. I have found this symptom sometimes of much service in diagnosis.

My own experience has been that in disseminated sclerosis, if sensation is impaired, *by far the most common form of impairment is loss of the vibrating sensation*, while other forms of sensation are felt; and that this condition is met with in a large proportion of the cases.

In *tabes dorsalis* at the very early stage the vibrating sensation is sometimes lost on the legs though other forms of sensation (to touch, pain and temperature) are normal. Hence in the diagnosis of tabes at the earliest stage, when the symptoms are few and slight, loss of the vibrating sensation may be of diagnostic value as additional evidence in favor of this disease.

In *hematomyelia* when sensation for pain and temperature have been markedly affected the vibrating sensation has been found unaffected, though the gray matter has been destroyed at the seat of the disease. (Case recorded by Bing.)

In a case presenting typic symptoms of *syringomyelia* of twenty years' duration I found the vibrating sensation unaffected, though sensation for pain and temperature were lost.

In the various forms of *spinal syphilis*, and specially in Erb's chronic form—*syphilitic spastic spinal paralysis*—the vibrating sensation is sometimes lost on the legs at the early period before other forms of sensation have become affected.

In *compression myelitis* due to spinal *caries* at the earliest period often no anesthesia to touch, pain or temperature can be detected. In addition to pain in the back and root pains there may be only slightly impaired muscular power in the legs and slight changes in the reflexes; yet at this stage the vibrating sensation is often lost on the legs and anterior iliac spines, being then the only form of sensation impaired.

In *spinal meningeal tumor* loss of the vibrating sensation may be the first form of sensory loss, *i. e.*, at the early stage we may find loss of the vibrating sensation on the legs while sensation to touch, pain and temperature are then unaffected. We have often, in the development of the symptoms of spinal meningeal tumor, a brief period at first in which paresis or paralysis of the legs is detected, but the reflexes are normal. The knee-jerks are normal and no ankle-clonus and no Babinski reflexes can be detected, and sensation of touch, pain and temperature are felt readily. In such cases the question of hysteria or functional affections may arise. But at this period we may find the vibrating sensation lost on the legs, and this would then be a sign in favor of organic disease. In these cases a Babinski reflex is soon obtained, ankle-clonus develops and anesthesia to touch, pain and temperature is afterward detected below the lesion.

In *compression myelitis from injuries* to the spine, and in other forms of traumatic lesion of the spinal cord, the upper limit of the anesthesia produced often indicates the localization of the lesion.

In *incompletely* transverse lesions, however, the sensation for touch and pain may not be lost, but the vibrating sensation alone may be lost below the lesion (on the bones of the legs and on the abdomen). On the skin of the abdomen the vibrating sensation may then be used to determine the upper limit of the sensory dis-

turbance and may thus be of localizing value (as pointed out by Dr. Gordon Holmes.[1])

In *cerebral* diseases I have never found the vibrating sensation affected alone or before other forms of sensation. When other forms of sensation are lost the vibrating sensation may also be lost, but it appears to be affected to a less extent than sensation to touch, pain or temperature. Also in recovery from anesthesia due to cerebral disease the vibrating sensation appears to return before other forms of sensation.

In *hysteria, functional affections, neurosis, neurasthenia and malingering* I have never found the vibrating sensation lost when other forms of sensation were unaffected or unaffected after suggestion. In any case of paresis or paralysis of the legs, if the vibrating sensation is lost while other forms of sensation are recognized readily, and if the patient persists in this statement in spite of suggestions to the contrary by the wording of the questions, then hysteria or malingering is very improbable. In these conditions if the vibrating sensation is lost other forms of sensation will also be affected, or after suggestion, by the form of the questions, the patient will state that they are affected.

In a case of *localized paralysis* in a limb, if the vibrating sensation is lost and other forms of sensation are felt, or lost, a lesion of a peripheral nerve or nerve trunk can be excluded as the cause of the paralysis. In a case of localized paralysis, if the vibrating sensation is lost and other forms of sensation are recognized, and the patient persists in this statement in spite of suggestions to the contrary, then hysteria or malingering is very improbable.

In any case of *hemianesthesia*, if the vibrating sensation is not felt when the foot of the vibrating tuning-fork is placed on the edge of the sternum on the side of the tactile anesthesia, but felt when placed at a corresponding point on the other side, the case is one of hysteria or functional disease or malingering. (When the vibrating sensation is felt when the vibrating tuning-fork is placed on either side of the sternum no conclusion can be drawn from this fact as to the diagnosis.) In cases of hemianesthesia due to organic disease, if sensation is impaired over the sternum at all, when the tuning-fork is placed over the half of the sternum on the anesthetic side the vibrations would be transmitted across to the other half of the sternum and would at least be felt there. In all cases examined by myself, if due to organic disease, the tuning-fork vibrations have been felt when the tuning-fork has been placed on either half of the sternum.

The vibrating sensation may also be of service in a similar manner in the diagnosis between functional and organic *anesthesia limited to a portion of a limb*, as I have elsewhere described in the following words:[2]

[1] British Med. Jour., November 29, December 4 and 11, 1916.
[2] Rev. Neurol. and Psych., November and December, 1918.

In *tabes dorsalis* at the very early stage the vibrating sensation is sometimes lost on the legs though other forms of sensation (to touch, pain and temperature) are normal. Hence in the diagnosis of tabes at the earliest stage, when the symptoms are few and slight, loss of the vibrating sensation may be of diagnostic value as additional evidence in favor of this disease.

In *hematomyelia* when sensation for pain and temperature have been markedly affected the vibrating sensation has been found unaffected, though the gray matter has been destroyed at the seat of the disease. (Case recorded by Bing.)

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In the various forms of *spinal syphilis*, and specially in Erb's chronic form—*syphilitic spastic spinal paralysis*—the vibrating sensation is sometimes lost on the legs at the early period before other forms of sensation have become affected.

In *compression myelitis* due to spinal *caries* at the earliest period often no anesthesia to touch, pain or temperature can be detected. In addition to pain in the back and root pains there may be only slightly impaired muscular power in the legs and slight changes in the reflexes; yet at this stage the vibrating sensation is often lost on the legs and anterior iliac spines, being then the only form of sensation impaired.

In *spinal meningeal tumor* loss of the vibrating sensation may be the first form of sensory loss, *i. e.*, at the early stage we may find loss of the vibrating sensation on the legs while sensation to touch, pain and temperature are then unaffected. We have often, in the development of the symptoms of spinal meningeal tumor, a brief period at first in which paresis or paralysis of the legs is detected, but the reflexes are normal. The knee-jerks are normal and no ankle-clonus and no Babinski reflexes can be detected, and sensation of touch, pain and temperature are felt readily. In such cases the question of hysteria or functional affections may arise. But at this period we may find the vibrating sensation lost on the legs, and this would then be a sign in favor of organic disease. In these cases a Babinski reflex is soon obtained, ankle-clonus develops and anesthesia to touch, pain and temperature is afterward detected below the lesion.

In *compression myelitis from injuries* to the spine, and in other forms of traumatic lesion of the spinal cord, the upper limit of the anesthesia produced often indicates the localization of the lesion.

In *incompletely* transverse lesions, however, the sensation for touch and pain may not be lost, but the vibrating sensation alone may be lost below the lesion (on the bones of the legs and on the abdomen). On the skin of the abdomen the vibrating sensation may then be used to determine the upper limit of the sensory dis-

turbance and may thus be of localizing value (as pointed out by Dr. Gordon Holmes.[1])

In *cerebral* diseases I have never found the vibrating sensation affected alone or before other forms of sensation. When other forms of sensation are lost the vibrating sensation may also be lost, but it appears to be affected to a less extent than sensation to touch, pain or temperature. Also in recovery from anesthesia due to cerebral disease the vibrating sensation appears to return before other forms of sensation.

In *hysteria, functional affections, neurosis, neurasthenia and malingering* I have never found the vibrating sensation lost when other forms of sensation were unaffected or unaffected after suggestion. In any case of paresis or paralysis of the legs, if the vibrating sensation is lost while other forms of sensation are recognized readily, and if the patient persists in this statement in spite of suggestions to the contrary by the wording of the questions, then hysteria or malingering is very improbable. In these conditions if the vibrating sensation is lost other forms of sensation will also be affected, or after suggestion, by the form of the questions, the patient will state that they are affected.

In a case of *localized paralysis* in a limb, if the vibrating sensation is lost and other forms of sensation are felt, or lost, a lesion of a peripheral nerve or nerve trunk can be excluded as the cause of the paralysis. In a case of localized paralysis, if the vibrating sensation is lost and other forms of sensation are recognized, and the patient persists in this statement in spite of suggestions to the contrary, then hysteria or malingering is very improbable.

In any case of *hemianesthesia*, if the vibrating sensation is not felt when the foot of the vibrating tuning-fork is placed on the edge of the sternum on the side of the tactile anesthesia, but felt when placed at a corresponding point on the other side, the case is one of hysteria or functional disease or malingering. (When the vibrating sensation is felt when the vibrating tuning-fork is placed on either side of the sternum no conclusion can be drawn from this fact as to the diagnosis.) In cases of hemianesthesia due to organic disease, if sensation is impaired over the sternum at all, when the tuning-fork is placed over the half of the sternum on the anesthetic side the vibrations would be transmitted across to the other half of the sternum and would at least be felt there. In all cases examined by myself, if due to organic disease, the tuning-fork vibrations have been felt when the tuning-fork has been placed on either half of the sternum.

The vibrating sensation may also be of service in a similar manner in the diagnosis between functional and organic *anesthesia limited to a portion of a limb*, as I have elsewhere described in the following words:[2]

[1] British Med. Jour., November 29, December 4 and 11, 1916.
[2] Rev. Neurol. and Psych., November and December, 1918.

"If the anesthesia is limited to a portion of a limb or one portion of the body, and if a long bone such as the tibia, ulna, femur or sternum is situated partly in the anesthetic area and partly in the non-anesthetic area, then the following test is occasionally of diagnostic service: If we find that the vibrating sensation is not felt *anywhere*, when the foot of a large vibrating tuning-fork is placed on a subcutaneous part of the bone just within the area of anesthesia, but the vibrations are felt when the foot of the vibrating tuning-fork is placed on the subcutaneous part of the bone just outside the area of cutaneous anesthesia, then the case is one of functional anesthesia (hysteria, malingering or 'idea' anesthesia). (If the vibrating sensation is not felt at both these points, no conclusion can be drawn from this symptom alone.)

"In the normal condition, when the foot of a large and suitable vibrating tuning-fork is placed on the subcutaneous surface of one end or one part of a bone, the vibrations are transmitted all over the bone, and are felt, though with diminished intensity, at distant parts of the bone. Hence if the foot of the vibrating tuning-fork is placed on the bone just within the limit of the anesthesia, though the vibrating sensation may not be felt at that point, the vibrations will be transmitted to other parts of the bone and should be felt there if the vibrating sensation of the other part or parts is not lost. It we find, therefore, that the vibrating tuning-fork is felt just outside the limit of the anesthetic area, this indicates that the vibrating sensation is not lost in the bone at this point, and therefore the transmitted vibrations should be felt *there* when the foot of the vibrating tuning-fork is placed within the anesthetic area."

In a case of *pernicious anemia* I have found the vibrating sensation lost though no other indications of lesion of the nervous system could be detected, but the patient complained of a sensation of numbness in the legs. (Probably spinal changes were commencing.)

In cases of *gangrene* of the toes associated with diabetes mellitus, and in cases of *perforating ulcer* of the foot associated with tabes or diabetes mellitus, we often find the vibrating sensation lost on the legs. The loss of this sensation is then due not to the gangrene or perforating ulcer but to the diabetes or tabes.

The remarks which I have made are sufficient to show the value of the vibrating sensation in the diagnosis of nervous diseases and to indicate that it is desirable to test this sensation in all cases in which a detailed examination of the nervous system is undertaken.

The following are common combinations of early signs of organic disease:

1. Loss of the vibrating sensation on the legs, slight incoördination, Babinski reflexes. (Later signs of ataxic paraplegia or combined posterolateral sclerosis or degeneration.)

2. Loss of the vibrating sensation on the legs or on the abdomen and legs or on the abdomen only. Babinski reflexes, loss of abdominal reflexes. (Later signs of disseminated sclerosis.)

3. Girdle pains, often for a long period; then loss of vibrating sensation on the legs, with Babinski reflexes. (Later signs of compression myelitis from tumor of the meninges or vertebræ.)

4. Loss of the vibrating sensation, loss of the tendo-Achillis reflexes, pain in the legs. (Later loss of knee-jerks and other symptoms of peripheral *multiple* neuritis.)

THE RELATIONSHIP BETWEEN CENTRAL AND PERIPHERAL INVOLVEMENT OF THE CRANIAL NERVES.*

By Ernest Sachs, M.D.

PROFESSOR OF CLINICAL NEUROLOGICAL SURGERY, WASHINGTON UNIVERSITY MEDICAL SCHOOL, ST. LOUIS, MISSOURI.

In the brief time assigned to me it is obviously impossible to deal with all the symptoms caused by endocranial involvement of the cranial nerves. I have therefore selected for consideration some of the symptoms of cranial nerve involvement which present unusual difficulties in diagnosis and about which our knowledge is still incomplete. I propose to confine my remarks to the first, second and eighth nerves and those portions of the fifth and ninth nerves which are concerned with taste. In other words, I am going to consider the cranial nerves that control the special senses in which you are particularly interested.

The various studies that have been carried on to locate the cerebral centers controlling the special senses have cleared up many points that have hitherto been shrouded in mystery, but there still remain a goodly number on which light needs to be thrown. But whether the loss of one of these functions is due to destruction of the end-organ, the cerebral pathways or center is still often most perplexing. *You* see a large number of such cases where we see one. If it would be possible to create a uniform method of study of all such cases, then a Gunn, a Helmholtz or a Hughlings-Jackson, or even a lesser light, might take this vast material, which both in quality and quantity has never hitherto been dreamed of, and cull from it most valuable information. The study of these special senses is beset with unusual difficulties, for here we are dealing with sensory phenomena which are difficult to throw light upon by any experimental observations on animals, since obviously

* Read before the Section on Instruction of the American Academy of Ophthalmology and Oto-laryngology, Philadelphia, October 19, 1921.

indirect methods must be employed to determine a disturbed function in an animal.

The anatomist has quite outstripped the physiologist in this field, for the course of the fiber connections for the most part is quite well known. There are three methods of studying the physiology of these special senses in animals. The first method consists in destroying a portion of the brain and noting whether the animal no longer reacts to a certain sensory stimulus.

In the second method similar observations are made on specially trained animals. An animal is trained to do a certain thing, let us say raise its right forefoot when a certain odor is presented to it, and then after some lesion has been produced one notes whether the animal still does this. This method has been carried out to a high degree of perfection by Kalischer, but there are inherent dangers in the method which throw doubt on its value. It presupposes, it seems to me, that these artificially developed reflexes are so firmly fixed in the animal's mind that a severe trauma, as removal of part of the cerebral cortex, will not influence them unless the function that is being studied is disturbed. Yet forgetfulness has at all times and in all ages been characteristic even of the human race. Even Homer records that the mere eating of the lotus fruit could produce complete amnesia. The pathway by which an artificial reflex is carried out can certainly be more readily inhibited than can the pathway that an animal has always possessed, as in the case of the sucking reflex or the bladder reflex. Therefore, when a certain stimulus does not lead to the reaction to which an animal has been trained, though it suggests that the stimulus is not appreciated, there is always a lurking suspicion which this method of investigation can never dispel that the acquired habit has been lost as a result of the trauma. In man after a severe cerebral injury it is a very common experience to find that the patient's memory for events of all sorts just preceding the accident is lost for weeks and often months. If this is true in man there is every reason why it should also be true in animals.

The third method has been to determine the presence or absence of a salivary reflex when a strong sensory stimulus is produced. This reflex can be elicited with the greatest ease in experiments on monkeys when the anesthetic becomes light, as I have been able to demonstrate to my own satisfaction repeatedly. It therefore makes me feel that the method is too unreliable to be seriously considered.

Up to the present time, therefore, the results of such investigations on animals, many of them very elaborate and careful, have had the serious handicap of uncertainty. I am convinced that the next real advances will be made when accurate clinical observations are subjected to the acid test by research students.

The more careful study and interpretation of subjective sensations, which of course can only be done on human beings, it has seemed to me would lead to advances in this field. By subjective sensations is meant those peculiar phenomena in which a patient complains of certain sensations which are not susceptible of other proof than the patient's assertion. Thus he may say he thinks he smells certain odors when there is nothing around to produce them, or he hears or sees or tastes something when the stimulus to produce these is not present.

The difficulties of the problem are nowhere better illustrated than in the olfactory mechanism. So little is really known on this subject that von Bechterew in his three volumes on the functions of nerve centers devotes but ten pages to the entire subject.

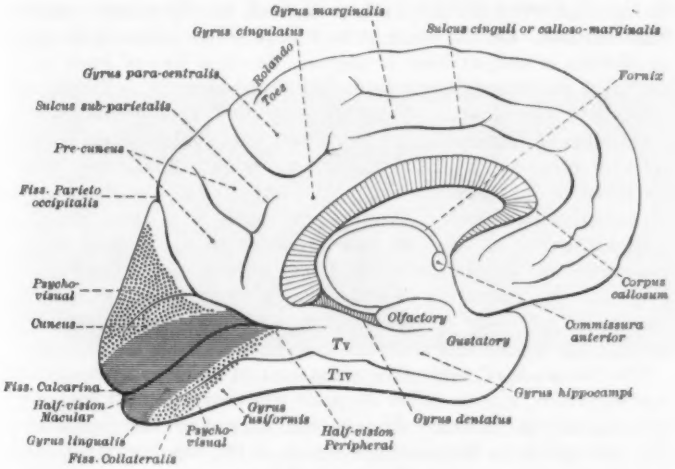

FIG. 1.—From Purves Stewart.

It is now quite generally conceded that the olfactory mechanism after leaving the olfactory bulbs at the base of the frontal lobes passes *via* the fornix to the gyrus uncinatus and pyriformis of the hippocampal lobe (Fig. 1). There is another group of fibers, the fibers of Lancisi, less well developed but of considerable size, which belongs to this mechanism. Our interest lies in differentiating smell disturbances if possible when they occur in these various regions. A lesion in the nose causes loss of all forms of smell, and so does a lesion in the olfactory pathways in the nervous system, unless the lesion, instead of being destructive, is irritative in character. This can be caused by an inflammatory process or merely when there is pressure on the hippocampal lobe; in such a case the patient experiences subjective sensations of smell. I have

believed that the presence of a subjective sensation of smell always means a hippocampal lesion, yet rhinologists have observed patients with this symptom with apparently only a nasal lesion. I know of no instance, however, in which such a case with the lesion supposedly in the nose has had its brain studied. Such studies would be essential to clear up this point. Is the loss of smell resulting from a nasal lesion the same as from a central lesion? Is the recognition of certain odors more inhibited in a peripheral lesion than in a central one? Does unilateral loss of smell occur with a lesion in one hippocampal lobe? How is the power to perceive an odor without the ability to name it to be interpreted? Do fluctuations in the sense of smell occur with lesions in one portion of the tract and not in the other?

Most of these questions still need further elucidation. A lesion in the nose when it leads to loss of smell usually causes complete bilateral loss. On the other hand, a destructive lesion of the gyrus pyriformis is said, at least in animals, to cause loss of smell in the nostril of the same side and some diminution of smell on the opposite side. The examination of the sense of smell is so uncertain even on intelligent human beings that tests on animals even by such eminent observers as Ferrier, Luciani and von Bechterew cannot be relied upon, especially when the latter claims to have noted unilateral *diminution* of the sense of smell in a dog. That the uncinate gyrus at least at times controls smell on both sides is illustrated by a case on which I was able to make careful tests (Fig. 2). No sensation of smell was present on either side, yet the lesion was only in one hippocampal lobe and his peripheral mechanism seemed normal.

The presence of subjective sensations of smell is evidence of a cortical lesion, the so-called uncinate fits that are most frequently encountered in pituitary disease, but there our knowledge ends. We are unable to distinguish a lesion of the olfactory bulbs from a lesion in the nose, nor do we know how to recognize a lesion of the fornix or the fibers of Lancisi.

A further point of great interest is how much reliance we may put on the ability of a patient to name odors as contrasted with his ability to recognize the presence of an odor without naming it. Does the naming of an odor constitute more of a mental process, and if it does, is this controlled by a different portion of the brain? If there is any occupation in which the olfactory sense is specially trained as tasting is in tea-tasters or the ear in a musician, the study of a pathologic lesion in the hippocampal lobe in such a patient might be of tremendous value.

The known facts in regard to taste are no more certain; in fact, the incontrovertible evidence is practically negligible. Even the peripheral portion of the mechanism offers difficulties of interpretation, and one wonders what the biologic significance of having

two peripheral pathways for carrying impulses of taste may be; the important role that taste plays in digestion may be the cause of this extensive peripheral nerve supply.

The taste fibers passing through the fifth nerve and those in the ninth carry the same sensations, and any differentiation is controlled in the cerebral portion of the pathway. About the ultimate cerebral terminations of the fibers there is much uncertainty, and in this instance the doubt is anatomic as well as physiologic. One group of observers believes the cortical center for taste lies in the hippocampal lobe nearer the convexity of the hemisphere (Fig. 1), while another group believes the center lies in the operculum near the motor center which controls the movements of the tongue and lips (Fig. 3). The most important investigation of this subject has been carried out in von Bechterew's laboratory by several of his assistants. A critical analysis of their work inevitably leads one to the conclusions that testing taste on animals is very

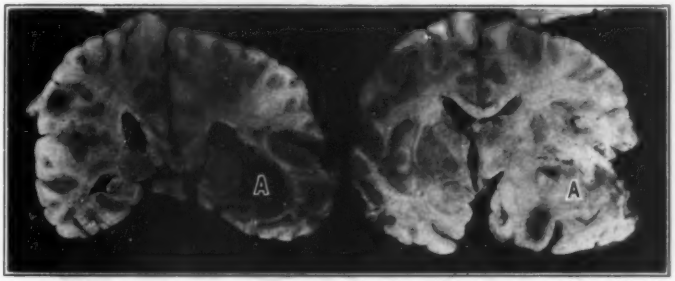

FIG. 2.—The tumor was an infiltrating glioma located at "A."

uncertain. These investigators have concluded that there is more or less marked diminution in the sense of taste and that this *diminution*—not loss, I would have you note—is more marked on the side opposite the lesion than on the same side. Such fine distinctions I feel confident are not possible in animals, since at least in my experience they are hardly ever possible in human beings. Furthermore, all taste tests to be reliable should be carried out with the patient's tongue protruded, since substances diffuse so rapidly on the moist tongue. In these experiments the test substances were introduced with a pipette on one or the other side of the tongue. The clinico-pathologic evidence is excessively meager, so that we are inevitably led to the conclusion that further studies on the sense of taste are urgently needed if we are to be able to make use of these sensory phenomena in more accurately determining the significance of disturbances in taste.

I have thus far dealt with the two special senses about which we know the least. Fortunately our knowledge of sight and hearing

is far greater; in fact, the mass of evidence, both experimental and pathologic, is so huge that a clear analysis of all this work would take much longer than is possible here.

I shall therefore select certain phases which bear particularly on the question of differentiating peripheral from central lesions.

1. Disturbances of ocular movements.
2. Disturbances of vision.

The movements of the eyes are controlled by the third, fourth and sixth nerves and their nuclei in the pons. Movements of the eyes can also be brought about by stimulation or destruction of the anterior corpora quadrigemina, that portion of the optic thalamus known as the pulvinar, the occipitotemporal region of the cortex and a center in the second frontal convolution (Fig. 4.).

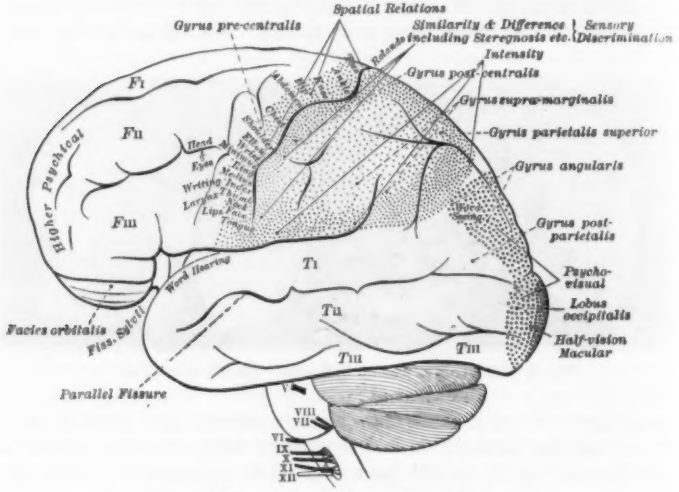

FIG. 3.—From Purves Stewart.

Though we are dealing here with motor phenomena these movements form such an intimate part of the visual mechanism that I feel justified in considering them.

The characteristic picture of an ophthalmoplegia needs no consideration here. The differentiation of irritative lesions of the peripheral nerves from lesions of the cerebral regions just mentioned, offer however, a real problem.

Experimentally it has been shown that stimulation of the anterior corpora quadrigemina brings about a spasm of accommodation and conjugate deviation of both eyes to the opposite side. This conjugate deviation may be to the side, upward or downward, depending on which portion of the quadrigeminal body is stimu-

lated; marked convergence of both eyes can also be brought about by stimulation of this region. All these movements can also be produced by stimulating the occipital cortex, the frontal region and the optic nerve, but if the corpora quadrigemina are destroyed stimulation of the occipital lobe no longer produces these movements, though they still can be produced by stimulation of the frontal center.

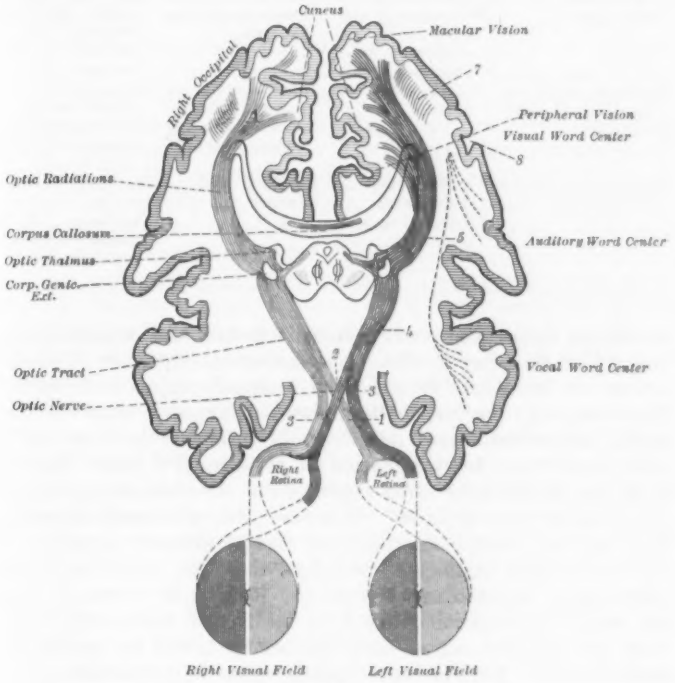

FIG. 4.—From Purves Stewart.

This is clear evidence to physiologists that the corpora quadrigemina are merely reflex centers and not primary centers, but this explanation does not materially help the clinician to differentiate lesions of these various regions.

Is our knowledge of these various regions adequate to enable us to recognize when they are diseased, and if so what are the salient points? That most accurate differentiation would be of great value is illustrated by the common example of conjugate deviation of the eyes which is noted in cerebral hemorrhage due to vascular disease and cerebral hemorrhage due to trauma.

When the symptoms are compared in parallel columns the dif-

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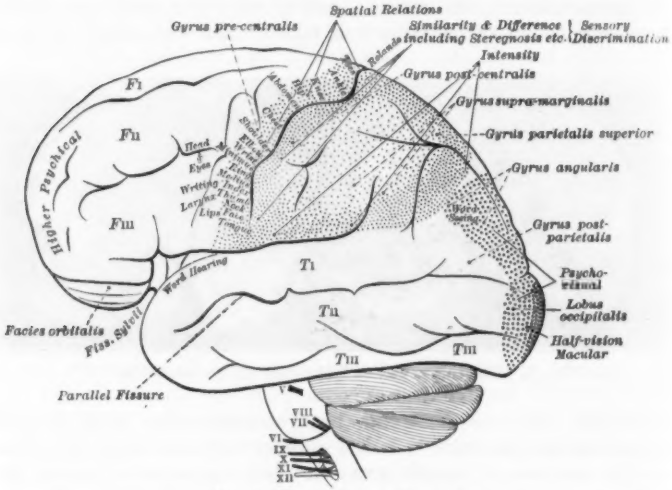

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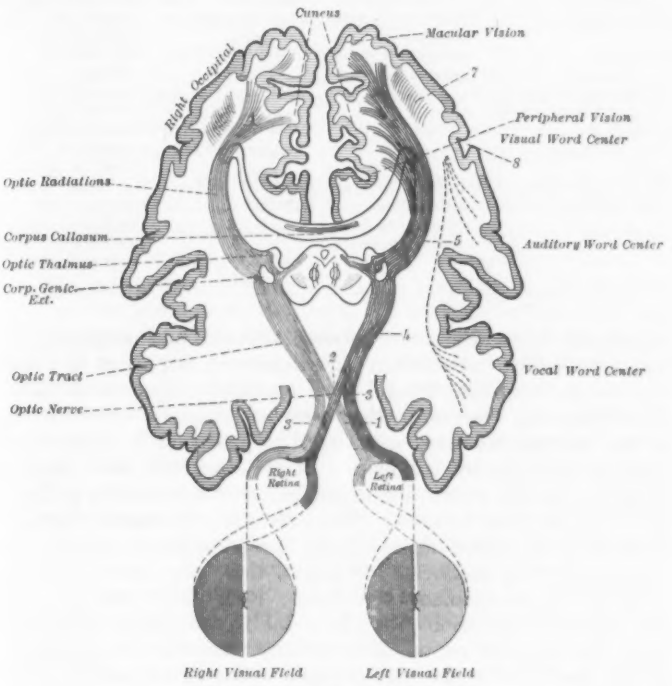

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When the symptoms are compared in parallel columns the dif-

ferences seem (see table) quite clear, but when applied to a particular clinical case the problem is by no means simple. For example, the

Frontal.	Occipital lobe.	Anterior corpora quadrigemina.	Optic nerve.
Conjugate deviation of the eyes. Vision intact.	Conjugate deviation of the eyes. Homonymous hemianopsia or homonymous visual impressions.	Conjugate deviation of the eyes. Homonymous hemianopsia.	Partial, complete or no ophthalmoplegia depending on involvement of 3d, 4th or 6th nerves.
Weakness or twitching of face of opposite side.	No motor involvement.	Hemiparesis or no motor disturbance depending on size of lesion.	Blindness of one eye or contraction of field depending on degree of involvement of nerve.
Pupillary reflexes undisturbed.	Pupillary reflexes undisturbed. Cortical blindness (Seelenblindheit).	Pupillary reflexes abolished.	No motor involvement. Pupillary reflexes abolished if blindness complete.

significant differential point between a frontal and occipital lesion is a field defect, but so often unconsciousness is present to thwart one in distinguishing frontal from occipital conjugate deviation. Experimentally Gerver, in Bechterew's laboratory, observed that ocular movements were more readily produced by frontal-lobe stimulation than by stimulation of the occipital lobe. How to make use of this interesting experimental observation in a clinical case I am at a loss to know. There are a few associated symptoms that may be helpful in clarifying these confusing pictures. If, associated with conjugate deviation, there are irritative motor phenomena, Jacksonian convulsions, it is more probable that the conjugate deviation arises from the frontal region rather than from the occipital region, since the frontal center lies so near the motor cortex. On the other hand, visual hallucinations would point rather to an occipital lesion, while the presence of high temperatures must always suggest the possibility of a ventricular involvement and consequently a lesion of the corpora quadrigemina, which protrude into the ventricle. The evidence of so-called heat centers in the brain is not to my mind conclusive in spite of the extensive studies of Barbour. In some unpublished experiments carried on in my laboratory by Captain Philip Green the evidence was not so positive that we felt convinced of the existence of a heat center or of its definite location. In other words, we are in the strange situation that though knowing quite accurately the functions of some of these centers we are often unable to determine by our present methods which center is involved.

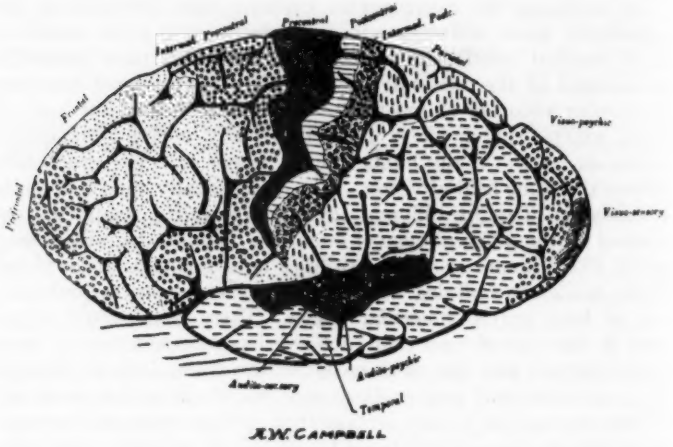
The act of vision, to which we turn next, would seem to be a sub-

ject in which most if not all the problems had been solved. I know of no other subject on which the concentrated efforts of such a group of great minds has been focussed. To name but some of these investigators: Flourens, Munk, Ferrier, Goltz, Luciani, Hitzig, Monakow, Bechterew and your honored guest from Holland. Yet there are a number of questions that still are unsettled.

In weighing the experimental evidence and determining the apparently great differences in some results, one point seems to have received insufficient attention, namely, that most mammals on account of the anatomic position of their eyes have complete monocular vision or at most partial binocular vision, but none of them except the monkeys have practically complete binocular vision as occurs in the human being, where each eye practically covers the same field of vision. The diametrically opposite results obtained on dogs by different investigators might readily be explained by the different type of dog used. Thus a dog with a long snout, like a hound or setter, can have no overlapping of his visual fields, while the bull-dog with the abbreviated nose undoubtedly has at least partial binocular vision. There is no doubt whatever in the case of man that each eye has representation in each visual cortex, and the most recent observations indicate though it is not absolutely proven that each macula is only represented in one cortex. It is also certain that various types of homonymous hemianopsia are produced by lesions of one optic tract after it leaves the chiasm, and similar defects may be produced at various points along this pathway (Fig. 4). Though phases of these questions are not absolutely clear the most profitable fields for investigation are the functions of the visual cortex and its location. Combining the anatomic studies of Campbell and Brodmann with the physiologic observations we know that the occipital region contains the cortical center of vision and that this area overlies Gennari's streak (Fig. 4,"A"), but what the functions of this cortex are is a debatable question (Fig. 5).

Von Bechterew believes that there are two centers, one lying on the mesial surface and one on the convexity, and that each of these centers has two separate functions, one controlling the peripheral vision and the other central vision. He furthermore believes that the center on the convexity is a higher one than that on the mesial surface and that the loss of this function leads to what the Germans have called "Seelenblindheit", the inability to interpret visual impressions. An integral part of this conception is the ability to interpret written words and muscial notes. Apparently there is some further differentiation between the right and the left visual cortex, and one is forced to the conclusion that probably the left cortex in right-handed individuals plays a greater role in the interpretation of such visual impressions. In spite of these fairly well-established facts it remains difficult to differentiate

a lesion of the lateral geniculate body and the pulvinar from lesions in the optic radiation as they stream through Gennari's streak into the occipital cortex. Some observers claim that the geniculate body is more concerned with macular disturbances than the visual cortex, though the recent studies by Gordon Holmes



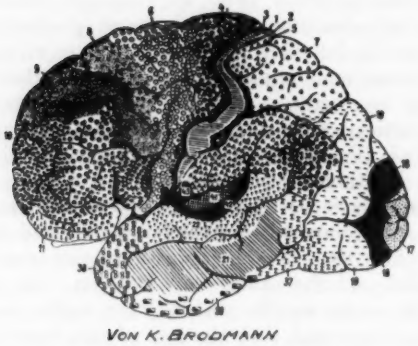


FIG. 5.—Areas of cortical function.

and by Lyster on gunshot wounds of the occipital region seem to establish the fact that the macula is represented in the cortex as is the rest of the retinal field, but each macula is represented in but one cortex—the cortex of the same side. There are those who feel that this question in regard to the macula is not yet proven. If it is so, however, the special function of the geniculate body

becomes more of a mystery than ever. We know that a lesion of this body produces a homonymous hemianopsia indistinguishable from a hemianopsia produced by lesion of the optic tract at various other points.

The interpretation and recognition of colors remains a still more uncertain question. The accepted theories of light perception all assume that the differentiation is carried out in the retina, but it seems that the cortex must exercise a further controlling influence. This is suggested by the cases in which subjective visual disturbances are noted during an attack of focal epilepsy which is due to an irritative focus in the occipital region. These rapidly passing color impressions that such patients experience are difficult to record. They are so rare that one observer rarely sees many, consequently the method of studying the phenomena is not uniform. Whether the succession of colors is always the same has as far as I know not been determined. On account of the intricacy of the problem we are offered here a most fascinating field for further investigation.

We come finally to a consideration of the sensations which are transmitted through the eighth cranial nerve. In considering these we must keep in mind that we are dealing with two separate and entirely distinct functions, those carried by the auditory portion and those by the vestibular portion.

The difference between the functions of the central and peripheral portions of the auditory mechanism is so much more clearly recognized than in the case of the other special senses that our attention is centered upon other aspects which offer greater difficulties in diagnosis.

1. The interpretation of those auditory impressions that are associated with speech and an appreciation of musical sounds.

2. The difference between disturbances of the median geniculate body, the posterior corpora quadrigemina and the auditory cortex.

The cases in which there is a partial impairment of hearing afford such opportunities for study. The first temporal convolution contains the auditory center; apparently it is divided into at least two portions, one of which controls tone and sound impressions while the other controls word impressions. Since man alone uses speech, the existence of this center in the posterior portion of the first temporal convolution can be only convincingly recognized by pathologic studies on human brains; the attempts to differentiate these centers in dogs, by supposing that howling is mere phonation, while barking, whining and snarling are akin to articulate speech, seem to me rather farfetched.

The appreciation of sounds, musical or otherwise, seems to be a bilateral cerebral function, while the *understanding* of language is confined to the left cortex in right-handed individuals.

This idea one does not at first readily accept, for speech seems

a far more universal attribute of man than does a musical sense; but a distinction must be drawn between the mere perception of sounds and the highly specialized development of the musical sense that is observed in musicians. This latter function seems to be confined to the left temporal convolution, as is speech, but the mere appreciation of sound has unquestionably bilateral representation. An individual can still hear sounds if his left auditory center is destroyed. The interpretation of auditory impressions, however, is carried out by the center in the left temporal lobe. In addition, a valuable diagnostic sign is the presence of subjective auditory phenomena. Such an individual may complain of hearing a variety of sounds or voices. These sounds may vary from time to time or always be the same. A patient with a localized tuber-

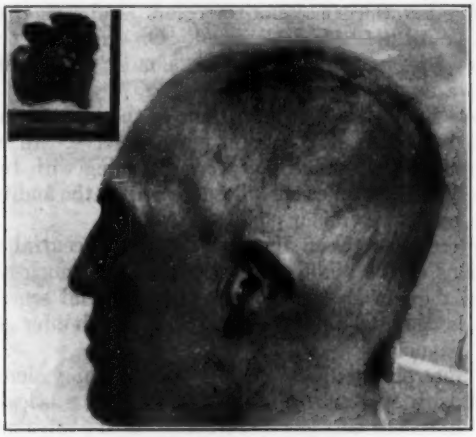


FIG. 6.—L. E. M. Surgical No. 7755. Tuberculoma, 4 x 5 cm. in size, removed from auditory speech center. Present eighteen years.

culous process, a solitary tubercle (Fig. 6), said that he had for years thought he heard church bells ringing. Just why he should have had only this subjective sensation when the greater part of his auditory center was involved is difficult to explain. For diagnostic purposes it is of great importance to keep in mind that immediately underneath the cortical center of hearing lies a region—Wernicke's field—in which the fibers from the olfactory, gustatory and auditory centers lie close to one another. In consequence an irritative lesion may produce subjective sensations arising from these three centers.

The functions of the median geniculate bodies and of the posterior corpora quadrigemina are by no means clear (Fig. 4). Gerver is of the opinion that through these centers movements of the eyes

and ears are probably brought about, but the evidence is not convincing. The best opportunity for studying these regions, particularly the posterior quadrigeminal bodies, may be found in observations on early cases of pineal gland tumor. In the few cases of this sort that have been studied no minute investigations that might elucidate this point have been carried on.

The posterior quadrigeminal body also has some connections with the vestibular portion of the eighth nerve. In some investigations in my laboratory with Dr. B. Y. Alvis we have found definite anatomic connections with Deiters's nucleus, but these studies threw no light on the vestibular function of the quadrigeminal body.

The importance of differentiating the central and peripheral portions of cranial nerves is brought home to us most strikingly when we note the enormous literature that has grown up about the vestibular portion of the eighth nerve. It is, I think, fair to say that practically the entire subject of neuro-otology occupies itself with this differentiation. Interest has been centered on the functions of the nerve tracts after they leave the labyrinth.

The finer movements of coördination are conceded to be functions of the cerebellum. Bárány has located certain centers for these movements in the lateral lobes of the cerebellum. His evidence comes primarily from the study of cases of cerebellar tumors in which after operation he has frozen the overlying skin with ethyl chloride and thus affected the cerebellum. Victor Horsley and Clarke showed how inert the cerebellar cortex was. Electric currents of great strength produced no symptoms that they could recognize. I noted no disturbances when I stimulated the cerebellum on a conscious patient some years ago. This of course does not mean that such centers do not exist. The methods of examination were different. The electric current has a stimulating effect while the freezing method has a temporary paralytic effect. My own observations on one patient have the further objection that the position of a patient lying on his face during a cerebellar operation is awkward for purposes of examination. Some recent clinical studies by Gordon Holmes on gunshot wounds of the cerebellum, however, do not support Bárány's contentions that there are separate centers in the cerebellum that control movements of the extremities. Any statement from such a careful observer as Holmes carries great weight. The pass-pointing and ocular movements that are produced by stimulation of the semicircular canals are not brought about by any one center but by interaction of several centers.

Movements of the eyes may be produced by action of the ocular nuclei, an area in the frontal lobe, the lateral geniculate bodies and the anterior quadrigeminal bodies; movements of the extremities are brought about by the anterior horn cells in the cord, by

the motor cortex and probably also by the cerebellum; vestibular stimuli are transmitted from Deiters's nucleus to the roof nucleus of the cerebellum, the olivary bodies, the posterior corpora quadrigemina. Through this maze of tracts and nuclei Jones and Mills have had the great courage to attempt to explain the mechanism by which the Bárány phenomena are produced (Fig. 7). Dr. Alvis and I have worked for several years with the idea of throwing

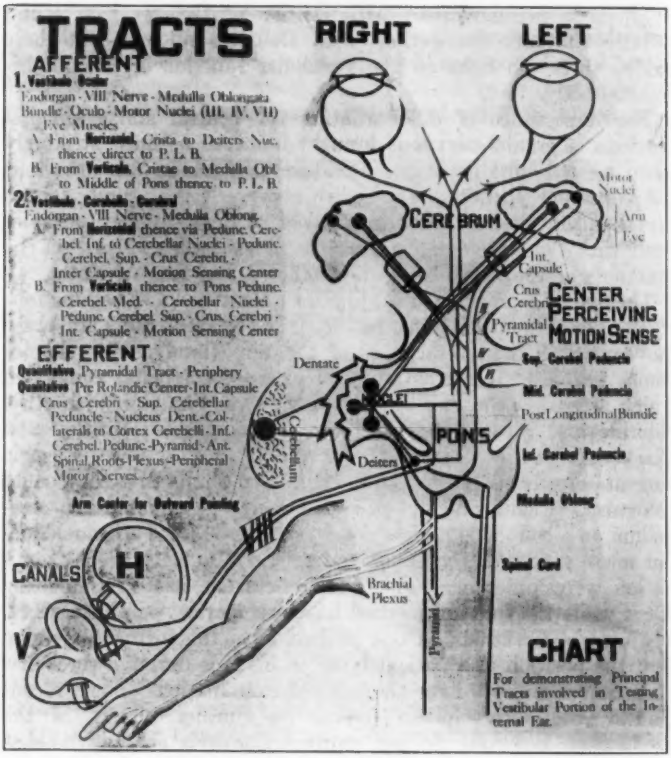

TRACTS
AFFERENT
1. Vestibule Center
Endorgan - VIII Nerve - Medulla Oblongata Bundle - Oculo - Motor Nuclei (III, IV, VI) Eye Muscles
A. From Horizontal Crista to Deiters Nuc. thence direct to P. L. B.
B. From Vertical Cristae to Medulla Obl. to Middle of Pons thence to P. L. B.
2. Vestibule - Cerebellar - Cerebral
Endorgan - VIII Nerve - Medulla Oblong.
A. From Horizontal thence via Pedunc. Cerebel. Inf. to Cerebellar Nuclei - Pedunc. Cerebel. Sup. - Crus Cerebri - Inter Capsule - Motion Sensing Center
B. From Vertical thence to Pons Pedunc. Cerebel. Med. - Cerebellar Nuclei - Pedunc. Cerebel. Sup. - Crus Cerebri - Int. Capsule - Motion Sensing Center
EFFERENT
Qualitative Pyramidal Tract - Periphery
Qualitative Pre Rolandic Center - Int. Capsule Crus Cerebri - Sup. Cerebellar Peduncle - Nucleus Dent. - Collaterals to Cortex Cerebelli - Inf. Cerebel. Pedunc. - Pyramid - Ant. Spinal Roots - Plexus - Peripheral Motor Nerves
Arm Center for Outward Pointing
CANALS
H
V
RIGHT
LEFT
CEREBRUM
Motor Nuclei
Arm
Eye
Int. Capsule
Crus Cerebri
CENTER PERCEIVING MOTION SENSE
Pyramidal Tract
Dentate
Sup. Cerebel Peduncle
Mid. Cerebel Peduncle
Post Longitudinal Bundle
PONS
Deiters
Cerebellum
Inf. Cerebel Peduncle
Medulla Oblong
Spinal Cord
Brachial Plexus
Pyramid
CHART
For demonstrating Principal Tracts involved in Testing Vestibular Portion of the Internal Ear.

FIG. 7.—Tracts involved in testing vestibular portion of the internal ear.

some further light on the anatomy and physiology of this problem. We believe our work confirms certain points, disproves some others, but leaves other questions in a rather unsettled state. We have found a definite connection between Deiters's nucleus and the posterior corpora quadrigemina. No fibers could be demonstrated passing from Deiters's nucleus to any of the lateral lobes of the cerebellum in which the centers described by Bárány lie. Isolated lesions of Deiters's nucleus (Fig. 8) or the vestibular nerve never

produce the violent circus movements which had come to be considered as a result of von Bechterew's work diagnostic of Deiters's nucleus lesions. Such movements when they occur always are due to a lesion of the neighboring inferior or superior cerebellar peduncles.

The connections between Deiters's nucleus and the ocular nuclei as described by Fraser were not demonstrable, so that the vestibulo-ocular phenomena must be brought about by a different pathway.

We were unable to determine whether the course of the fibers from the vertical and horizontal canals followed different pathways or not on their way to the roof nucleus of the cerebellum. Again, it was not possible to demonstrate, what on theoretical

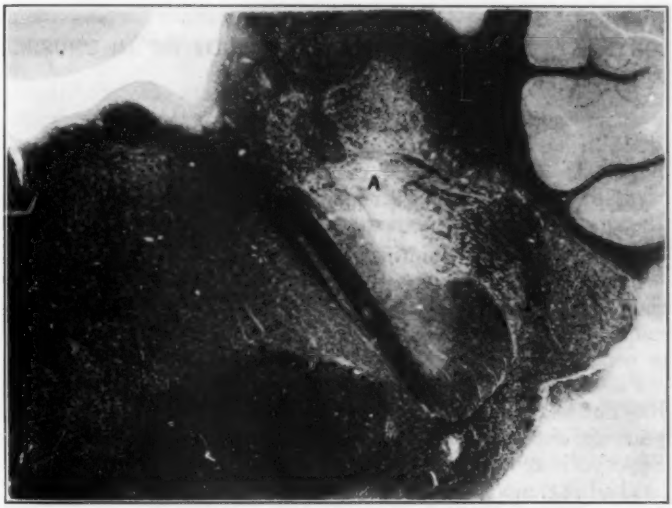


FIG. 8.—Lesion of Deiter's nucleus at A.

grounds we believe, that each semicircular canal is controlled by a separate group of cells in the Deiters's group. The most important single fact that has been established is that the tracts by which these phenomena are carried out lie immediately about the aqueduct of Sylvius and are therefore most easily affected by changes in intracranial pressure. Internal hydrocephalus is an almost invariable accompaniment of spreading processes in the posterior fossa, and the pressure of the obstructed cerebrospinal fluid frequently brings about the symptoms that have been considered evidences of local lesions. This complicating factor tends to make our knowledge of the functions of the different portions of the vestibular mechanism less certain than we have been led to believe.

If we consider for a moment what has been said this evening it must be apparent that I have passed over for the most part the facts that are well known and have tried to bring out in high relief some of the unfinished or thus far unanswered problems on the borderline of your specialties and neurology. To the earnest student these are the questions which it is most desirable to grapple with. The more difficult of solution the more worth while they are. The vast material that passes through the hands of the members of this organization contains within itself the evidence that will clear up these disputed points. To collect, correlate and subject to critical analysis all this material by uniform methods would be a fundamental and enduring service.

ORTHOSTATIC ALBUMINURIA: THE STUDY OF AN UNUSUAL CASE.*

By Wyndham B. Blanton, M.D.,
RICHMOND, VIRGINIA.

Case History. Female, white, aged twenty-three years, single, school teacher.

Chief Complaint. Fainting.

Family History. Father living and well; mother died at forty-eight years of paralysis; one sister living and well; no brothers. No family history of rheumatism, gout, diabetes, cancer, tuberculosis or nephritis.

Past History. Patient has had the common diseases of childhood. Has not had scarlet fever, diphtheria or many sore-throats. Ten years ago she suffered with a suppuration of the glands of the neck. Eight years ago a chronically diseased appendix was removed. She has had pneumonia. Several years ago she contracted the "fever" in South America.

Personal History. Sleeps from 10 P.M. to 7.30 A.M. Is fond of outdoor exercise and takes more than the average quantity. Teaches school. Meals are regular; eats slowly, moderately and sparingly of meat. Drinks one cup of coffee a day. Menstruation established at twelve, regular, lasting four or five days. A moderate amount of pain precedes.

Present Illness. Has been given to fainting all her life. Fainted one month ago at the theater; again last night when she witnessed a harrowing picture; again today she felt that she was going to faint in school. Alarmed at the frequency of these attacks, she is seeking advice. She has recently lost some weight—from 106 to 95 pounds—and does not feel as strong as she did. She has also tingling in the hands and the feet.

* Read before the Richmond Academy of Medicine, November 8, 1921.

Cardiac. No disagreeable precordial sensations; no edema of the ankles; no palpitation.

Respiratory. Patient has had no cough, expectoration, dyspnea, pain in the chest or night-sweats.

Gastro-intestinal. Her appetite is fair, bowels regular, no abdominal pain, no indigestion, no jaundice, no piles.

Genitourinary. No nocturia, polyuria, headaches, visual disturbances.

Nervous System. No abnormal symptoms. Hearing is good; no dizziness.

Physical Examination. *General Appearance.* A slender and frail young woman, with more than average alertness, who does not hold herself well and tends, when in a sitting position, to slouch.

Constitutional Signs. Temperature, 98.3°; pulse, 72; respirations, 18. Weight, 97 pounds. Height, 5.5. Blood-pressure, 105/70.

Skin. Smooth, warm, moist, no cyanosis, jaundice or edema.

Head. Scalp clean. Eyes: pupils dilated, round, equal, regular, react well to light and accommodation; globes move well in every direction. Nose: partial obstruction of right nostril. Ears: no discharge, no mastoid tenderness, hearing normal. Mouth: teeth good; tongue clean, straight, no tremors; pharynx and tonsils slightly congested.

Neck. Large scar on left side following removal of cervical gland some years ago.

Lymph Glands. No enlarged axillary, inguinal or epitrochlear glands. Cervical gland removed some years ago.

Thorax. Narrow and long, expands uniformly with respiration. Lungs: resonant throughout, no rales, no change in voice or breath sounds. Heart: normal in position and size, no murmurs, no thrills or abnormal impulses, sounds of good quality. Pulses equal, regular, and of good force.

Abdomen. Symmetrical, flat, muscles somewhat tense; liver, spleen and kidneys not felt; no masses, no tenderness except on right over old operative scar.

Spine. Examination of the back, by Dr. Wheeldon, standing, shows left shoulder higher, left scapula above the line of the right scapula, left hip prominent, with left total curvature of the spine. There is some rotation of the spine backward to the right. There is no limitation of motion; in flexion or hyperextension, but lateral motion shows a definite stiffness in the lumbar spine when bending to the right and a stiffness in the lower dorsal spine upon bending to the left. Total bending of spine to the right and left does not seem much limited. Patient's posture is bad, showing a definite rounding of the thoracic spine, with some compensatory lordosis of the lumbar spine. Pelvis is tilted forward with protrusion of abdomen to some extent. Examination, lying, shows hyper-

extension to be normal. Legs are of the same length. No limitation of motion at the hips.

Extremities. Negative.

Neurological. Cranial nerves normal, motor power normal, sensation normal; no ataxia; equilibrium normal; reflexes active.

Fluoroscopic Examination. Diaphragm and bony outlines of chest normal; pulmonic fields illuminate well; no increase in bronchial markings; aorta normal. Heart: normal in midline position.

Czermac's sign positive on both sides. Pulse slowed, 108 to 80. Patient fainted when blood was withdrawn from arm, and cardiac rate on auscultation was about forty. Eye-grounds negative.

Laboratory Reports:

Blood Count. White blood cells, 8800; polynuclears, 77 per cent; red blood cells, 4,400,000; hemoglobin, 85 per cent.

Urine. Amber; acid; clear; 1018; no sugar; heavy trace of albumin; no mucus, pus or blood; occasional hyaline cast; repeated thirty-five times with practically the same results.

Urine Chlorides. 5 gm. twenty-four hours.

Mosenthal. Night, 350 cc; day, 773 cc; greatest difference in specific gravity, 20.

Wassermann. Not done.

Blood-sugar. 104 mgm. per 100 cc blood.

Blood Urea. 1st examination, 34 mgm. per 100 cc blood; 2d examination, 12 mgm. per 100 cc blood; 3d examination, 24 mgm. per 100 cc blood.

Phthalein. 1st examination, first hour 50, second hour 12; 2d examination, first hour 50, second hour 25.

Chemical Analysis of the Protein Fraction of the Urine: Night.—Serum albumin, 0.13 per cent. Serum globulin, 0.04 per cent. Nuclear protein, 0. Day.—Serum albumin, 0.13 per cent. Serum globulin, 0.04 per cent. Nuclear protein, 0.

Roentgen ray of spine at three levels showed no abnormality of any of the vertebræ.

EFFECTS OF POSTURE ON BLOOD-PRESSURE.

	Bl. P.	P. P.
Lying	130/80	50
Lying with pillow under back	130/90	40
Sitting	130/90	40
Standing	125/93	32

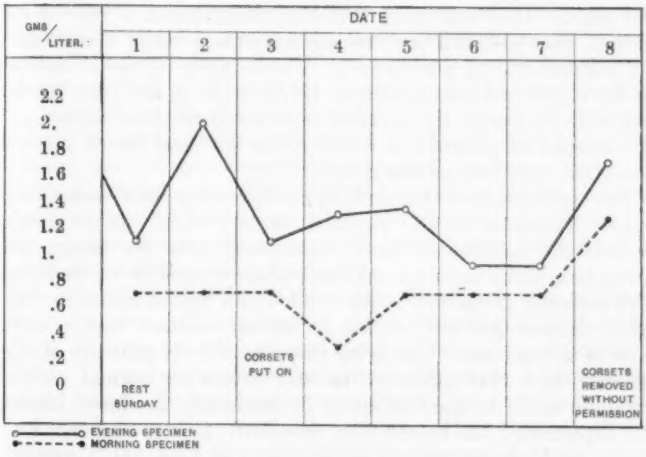
EFFECT OF DAY AND NIGHT ON ALBUMINURIA. DEGREE OF ALBUMINURIA.

Time.	1st day.	2d day.	3d day.
7.00 A.M.	Marked trace.	Trace.	Marked trace.
3.00 P.M.	.....	Faint trace.	Trace.
9.30 P.M.	Marked trace.	Marked trace.	Marked trace.

EFFECT OF REST ON ALBUMINURIA* (PATIENT KEPT IN BED FOR THREE WEEKS).

Day.	Gm. per liter of urine.
1	2
2	1
3	.3
4–21	.3–.5

EFFECT ON ALBUMINURIA OF WEARING LIGHT PLASTER JACKET ONE WEEK.



Diagnosis. 1. Syncope of vagal origin. 2. Albuminuria, orthostatic.

Discussion. The escape of coagulable proteins from the blood and their appearance in the urine are generally conceded, though not proved, to be due to an alteration in the glomerular tuft, resulting in the permeability of this structure for substances commonly called albumin. The occurrence of a coagulable protein in the urine (putting aside pus, blood, spermatorrhea, etc.) is common in disease and occasional in health. The acute and chronic diseases of the kidney characterized by albuminuria are well known. During what we consider as good health albumin not infrequently makes its appearance in the urine. Frequently albumin may appear in the urine after severe exercise, cold baths, mental strain or the ingestion of raw protein, such as egg albumen. Albuminuria of longer duration occurs in the newborn and in pregnancy (about 50 per cent). So-called essential albuminuria (Sahli[3]) may last for years and includes the albuminuria of adolescence (von Leube) and orthostatic albuminuria.

In describing the condition of orthostatic albuminuria various synonyms have been employed by different authors. It has been called also lordotic, intermittent, postural, cyclic and physiologic.

* Two months after getting out of bed albumin had again mounted to 2 gm.

To fulfil the diagnostic postulates generally given of this condition the patient must repeatedly show albuminuria in the erect position which disappears in recumbency. A few hyaline casts may or may not be present. Other evidence of nephritis must be excluded.

Roger I. Lee[4] in a discussion of albuminuria in healthy young men makes a threefold classification: (1) Those who show albumin only during the day—strictly postural albuminuria and including by far the largest number; (2) those who show small amounts of albumin occasionally; (3) those who show albumin in all specimens both day and night. It is our belief that this classification is correct and, further, that so-called postural albuminuria is really a subhead of the albuminuria of adolescence. These types represent different grades of the same disturbance. However, as in our case, the fact that with rest even the severest form tends to great reduction in the amount of albumin shows that the postural factor plays an important part here as elsewhere.

The explanation of this striking condition has been variously set forth. Foremost is the postural theory, which makes lumbar lordosis the mechanical factor interfering with the return renal circulation, which in turn is said to produce congestion of the kidney with sufficient glomerular stasis to allow of a leak of albumin. Since Jehle[3] showed that lordosis was an almost constant finding in this type of albuminuria, that lying down would rid patients of their albumin, and that albumin-free and otherwise normal children could be made to show albumin by artificially produced lordosis, this explanation has been widely accepted. Others supporting this theory are L. Jeanneret,[4] G. Pechowitsch,[5] K. Dietl,[6] G. Turrettini,[7] L. Piesen,[8] A. Lury,[9] R. Fischl,[10] H. Nothmann,[11] J. M. Hamelberg,[12] Roger I. Lee,[2] M. H. Bass,[13] L. F. Barber and F. J. Smith.[14]

Erlanger and Hooker[15] advanced another theory—that the diminished pulse-pressure occurring in these patients in passing from the reclining to the erect posture is responsible for their condition. They maintain that the normal difference in maximal and minimal pressure, or pulse-pressure, acts as a pounding force in the kidney, and to keep up the normal renal circulation, which is accompanied by no albuminuria, this range of variation in blood-pressure is necessary. The diminished pulse-pressure in the erect position, said to be characteristic of orthostatic albuminuria, therefore permits of renal congestion, and hence of albuminuria.

K. Dietl[6] assumes that these abnormal blood-pressure changes are based upon vasomotor instability. He has, however, given a name and not an explanation of this phenomenon. R. von Stejskal[16] holds to a similar explanation. Mason and Erickson[17] also champion this theory in a recent article illustrating their argument from five cases. Some authors have considered a floating kidney responsible for the urinary findings. The idea of Tissier[18] that this condition is due to a congenital histologic anomaly resulting in an increase of glomerular permeability has nothing in fact to substantiate it.

In the final analysis it appears that the best evidence goes to show

that the most probable explanation of postural albuminuria lies in lordosis, with or without vasomotor stigmata, in the constitutionally predisposed.

We are fortunately not without valuable statistical studies relating to the incidence of albuminuria in healthy adolescence, numerous authors having investigated exhaustively this phase of the subject.

Lee[2] found that 5 per cent of 5000 so-called healthy young men of college age showed albumin in the urine. Only 0.1 per cent of these had nephritis. Maclean[19] among British soldiers during training found 5 per cent of 50,000 examined with albuminuria. Of these, 3 per cent had only very slight albuminuria. Reber and Lauener,[20] in Switzerland, showed that of a battalion of 528 healthy soldiers examined, 10 per cent gave a reaction in the urine for albumin. Bugge[21] claims to have found 15 per cent of albuminuria among 1076 school children examined. Gotzky[22] in children also gives high percentages—among 346 examined, 14 per cent were the subjects of albuminuria. Hamelberg[12] also studied school children. Among 401 boys he found 8 per cent with albuminuria; among 311 girls, 22 per cent. Albuminuria in adolescence, therefore, is encountered with surprising frequency.

One in a thousand of Lee's[2] cases had albuminuria with evidence of kidney disease. Of Maclean's[19] 50,000 soldiers examined during training 132 subsequently entered the hospital with war nephritis, but only 17 per cent of these had shown albuminuria during their training period. Various authors have studied the functional capacity of the kidney in postural albuminuria. Their findings almost uniformly show the kidney free from the changes characteristic of nephritis.

Mason and Erickson[17] did "phthaleins" on 5 cases and Barker and Smith[14] report results of 6 patients similarly tested. There were no abnormal findings. Lee[2] found normal functional tests in his cases which were not nephritic. In 662 men, 12.8 per cent had a labile systolic blood-pressure of 140 or more due, it was thought, to nervousness. Among this group, however, he discovered albuminuria twice as often as among others with normal blood-pressure. Jehle[3] pointed out that albuminuric patients may show oliguria with low salt output while up and about, and that these abnormal findings disappear when these same patients are put to bed. Mason and Erickson[17] state that casts are usually absent. Lee[2] found them in 15 per cent of his cases. Maclean[19] claims, on the other hand, to have found casts in only 1.8 per cent of the 50,000 men he examined.

Sahli[1] quotes von Leube as stating that the age incidence of orthostatic albuminuria is between the fourteenth and eighteenth year. Mason and Erickson[17] quote Lommel as finding this condition chiefly between fifteen and twenty-one, while they themselves give sixteen to twenty-two as the period when it is most liable to appear. The great mass of the literature on the subject is given over to the study of this condition in school children. One of Mason and Erickson's[17] cases, however, was a man forty-three years old.

Barker and Smith[14] cite cases twenty-four and twenty-five years of age respectively. It may be stated then that while the condition occurs with fair frequency in adolescence it is distinctly uncommon after this age. The sexes seem to be equally affected.

So definite is the relation of these urinary findings to certain physical characteristics that most authors describe an orthostatic type of individual. These patients present physical characteristics of which lordosis and other spinal curvatures are but a single manifestation in a complex constitutional weakness or defect. They are nervous, anemic, lean and poorly nourished individuals, subject to vasomotor instability, ptoses and postural faults.

Most writers agree in assuming an optimistic outlook with reference to improvement, believing that the albuminuria itself is not a serious occurrence, related as it is to no known structural disease of the kidney. Treatment offers hopeful results. Lee[2] as well as others cite striking improvement with the vertebral brace, abdominal supports and lumbar muscle exercises.

SUMMARY. A case of persistent albuminuria in a young woman has been described. The history, physical examination and functional tests of the kidneys failed to show evidence of nephritis. Albumin persisted at the expiration of three weeks in bed, making it difficult at first glance to reconcile this case with the usual description of orthostatic albuminuria. However, the marked reduction of albuminuria (from 2 to 0.3 gm.) with rest and support of the back makes the condition clearly of the same general category of the postural or orthostatic albuminuria, though probably of a more severe grade than usually encountered. The evidence of a vasomotor disturbance in this patient has been brought out, and this additional factor may account for the persistence of albuminuria with rest.

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REVIEWS.

LESSONS IN PATHOLOGICAL HISTOLOGY. By GUSTAVE ROUSSY, Professeur Agrégé and IVAN BERTRAND, Chef de Laboratoire des Maladies Nerveuses, Université de Paris. Translated from the second French edition by JOSEPH MCFARLAND, Professor of Pathology and Bacteriology in the Medical Department of the University of Pennsylvania. Pp. 268; 124 engravings. Philadelphia and New York: Lea & Febiger, 1922.

FOR a work of its size, this small book contains a surprisingly large fund of information, clearly exposed in convenient form. Opposite each page of text is the corresponding illustration with very satisfactory descriptions. In most of the illustrations, however, the magnification is so small, that while details would doubtless be recognizable to one already familiar with the subject, it is questionable whether they would be of equal value to the beginner, for whom such a book is designed. Figs. 2, 46 and 64 are notable exceptions. Although the subject-matter is based upon the course given in the University of Paris, it does not, according to the preface, aim at a complete presentation, but rather to teach the student the correct method. As an accompaniment then to a more complete book, it should prove to be of value. K.

HAYFEVER AND ASTHMA: CARE, PREVENTION AND TREATMENT. By WILLIAM SCHEPPEGRELL, A.M., M.D., President, American Hayfever Prevention Association; Chief of Hayfever Clinic, Charity Hospital, New Orleans. Pp. 274; 108 illustrations. Philadelphia and New York: Lea & Febiger, 1922.

THIS book is an excellent contribution to the literature. From the standpoint of the etiology of hayfever and (as the title should more specifically read) hay asthma, it is the most complete statement of the subject available, representing as it does the result of years of work by the author and his associates in the American Hayfever Prevention Association. There is a survey of the hayfever producing plants, their distribution and period of pollination throughout the United States, with detailed descriptions and

illustrations of some of the most important. Over two hundred plants, including many that have been wrongly suspected of causing hayfever, have been investigated. There are tabulated for each state the local causes of hayfever, and, when they exist, "hayfever resorts"—localities in which the offending plants are scarce or absent. The botanic characteristics that make a plant a potential hayfever cause, namely, wind pollination—a pollen that is produced in large quantities, and whose grains are sufficiently small to permit of wide wind convection—are well demonstrated and emphasized. It is pointed out that hayfever is, in a measure, preventable and there are discussed educational and legislative measures for weed control, based on the gratifying results obtained under the author's guidance in New Orleans. The chapter on treatment is adequate. It is to be regretted, however, that the author has not gone into a little more detail as to treatment and results, perhaps with illustrative case histories. A disease that afflicts 1 per cent of the population demands the attention of every practitioner. The author's well written and profusely illustrated book can be highly recommended. R. A. K.

THE THYROID GLAND. By GEORGE W. CRILE, M.D., and Associates at the Cleveland Clinic, Ohio. Pp. 228; 106 illustrations. Philadelphia: W. B. Saunders Company, 1922.

THE purpose of this volume as stated in its introduction is to present the present theoretic and practical viewpoints of the author and his associates on the subject of the thyroid gland. It is admittedly but an ephemeral publication, and does not purport to be a textbook or a monograph and will be constantly subject to revision and possibly reversal of opinion. The book is composed of twenty-two separate articles, eight of which are at least in part written by the senior author; the others are by his associates in the Clinic staff. Several are highly theoretical and in their present brief form unconvincing. The rest are extremely practical and detailed, and their worth may be estimated from the fact that they represent the actual working methods of one of the most efficient surgical clinics in the world. Special mention must be made of the articles on the preoperative and on the postoperative treatment of the exophthalmic goiter patient. Throughout the book one finds a tendency to lay more stress on the so-called Goetsch test than is the rule elsewhere, and conversely less emphasis is placed on the estimation of basal metabolism. There is something in the book of value for every physician who is concerned with thyroid disease and there is much of value for every surgeon. This value is to be found in the practical rather than in the theoretical sections of the book. O. H. P. P.

DISEASES OF THE EYE. By MAY, Visiting Surgeon, Eye Service, Bellevue Hospital; Attending Ophthalmic Surgeon, Mt. Sinai Hospital, New York. Tenth Edition. Pp. 426; 377 illustrations. New York: William Wood & Company, 1922.

THIS manual describes the more common diseases of the eye at sufficient length to give one a clear idea of the etiology, symptoms and treatment. Where the pathology is important it is briefly discussed. The contents are arranged systematically, starting with a description of the different methods of examination.

The illustrations are excellent and include twenty-two plates, with seventy-one colored figures.

The chapter on "Disturbances of Motility of the Eye" is especially helpful because of its diagrams.

This book could be recommended as a manual, but should not be substituted for a text-book. H. W. S.

SURGICAL CLINICS OF NORTH AMERICA, VOL. II, NOS. 2, 3, 4. Pp. 820; 453 illustrations. Philadelphia: W. B. Saunders Company, 1922.

THESE three numbers, from San Francisco, Chicago and Boston, give the reader some most interesting and valuable information. The contributors are those standing among the highest in the profession and it seems as though these same writers have endeavored to put forth their utmost to present valuable articles. The contributions cover well the entire field of surgery, with the exceptions of the restricted specialties. Excellent articles are given on bone, joint, intestinal, kidney, tendon, hand and other subjects from both the surgical and pathologic standpoints.

I wish again to state here that the character of the *Clinics'* products is daily and rapidly approaching the really valuable clinical presentation, where padding with non-essential historical and clinical data is taboo, and only the essentials for diagnosis and treatment are noted. E.

MEMORIAS DO INSTITUTE OSWALDO CRUZ. Volume XIII, 1921.

This volume contains two valuable articles. One is entitled "Contribution to the Study of the Helminthologic Fauna of Brazil," by DR. LAURO TRAVASSO. The monograph deals especially with the morphology of the family Trichostrongylidæ, and comprises 140 pages fully illustrated with 56 plates and figures.

The other article is entitled "Observations upon Two Genera,

Urogonimus and a New Form of Leucochloridium, in a New Host," by Dr. Adolph Lutz. The writer believes this Leucochloridium to be a new species found in Brazil, and different from the Leucochloridium described by Montichelli in Europe and that described by Magath in America. R.

The Intestinal Protozoa of Man. By Clifford Dobell, M.A., F.R.S., National Institute for Medical Research, London; and F. W. O'Connor, M.R.C.S., L.R.C.P., D.T.M. and H., London School of Tropical Medicine. New York: William Wood & Company, 1921.

As the title indicates, this book represents the result of the observations and studies by the authors on the intestinal protozoan parasites of man as they are found in England, in which is included a review of the work of other investigators upon these parasites. The book is divided into nine chapters and consists of 221 pages and 8 plates.

A general introduction to the subkingdom protozoa and its four phyla, and descriptions of the known amebas (four genera and five species), flagellates (five genera and five species), coccidia (two genera and four species) and ciliates (two genera and three species) are given in separate chapters, which also include the pathology and symptomatology of the respective infections.

The outstanding feature of this book is the fact that in its preparation are combined the experience and efforts of a zoölogist and a medical man, as is clearly manifested in the character of the zoölogical and medical consideration of the subject discussed. The diagnosis and treatment of intestinal protozoal infections are discussed, in which the laboratory man and the clinician will find many helpful and valuable suggestions. The last chapter contains a very useful and practical discussion of the Coprozoic protozoa of man.

The authors may be criticized for their rather radical attitude in some features of the book, such as the description of the so-called *iodin cysts* in amebas (Dobell), which probably need further confirmation, as to the omission in the book of the description of Entameba paradysenteriæ (Chaterjee); of Entameba macrohyalina (Tobaldi); the statement that the cyst of Trichomonas hominis and the cultivation of this parasite *in vitro* has not been satisfactorily demonstrated; the doubt as to the existence of so many structures in the small cyst of Chilomastix mesnili (Kofoid and Swezy) and their view regarding the nuclear division. It should be borne in mind that these statements express the authors' personal experience. To be sure, they reflect a rather wholesome conservative attitude which is commendable in view of the tendency

to premature conclusions, often encountered, regarding the discovery of new facts or new species among protozoa.

The book, as a whole, is fairly complete, logical in its arrangement and precise in its description, and written in an attractive style. This work may be considered a valuable contribution to the study of the intestinal protozoa parasites of man, and will be found of great assistance to laboratory workers and physicians in the diagnosis and treatment of these infections. R.

STUDIES ON THE HISTORY AND METHOD OF SCIENCE, VOL. II. Edited by CHARLES SINGER. Pp. 559; 55 plates and 80 illustrations. Oxford: Clarendon Press, 1921.

As the title suggests, this is a collection of papers by various authors, containing reviews and discussions of the earliest application of scientific methods in the growth of medicine. There is a wealth of detail and a pleasing discussion in each chapter. It is impossible to enumerate in a brief space the wonderfully interesting and scientific data compiled here. The subject-matter covers chemistry, mathematics, physics, metaphysics, philosophy, botany paleobotany, religion and language.

The first and tenth chapters are written by Charles Singer, bearing the titles, "Greek Biology and its Relation to the Rise of Modern Biology" and "Steps Leading to the Invention of the First Optical Apparatus." The former is intensely interesting in a comparative analysis of the early Greek methods and the present-day investigations.

J. L. E. Dreyer contributes a pleasing history of "Mediæval Astronomy." The fourth chapter, written by Robert Steele, has an account of "Roger Bacon and the State of Science in the Thirteenth Century." One obtains a clear appreciation of the difficulties attending scientific pursuits at that time and marvels at the persistence of these pioneers in pursuing their investigations in spite of almost insurmountable opposition.

H. Hopstock portrays, from a translation from the Norwegian by E. A. Fleming, a study of "Leonardo as Anatomist." It is exceedingly well written and emphasizes the versatility and love of sciences of one of the greatest men of the ages. In the fifth chapter E. T. Withington discusses "Asclepiadæ and the Priests of Asclepius." The "Scientific Works of Galileo (1564–1642), with Some Account of His Life and Trial" is a thorough and clear review of Favaro's edition by J. J. Fahie. The thoroughness of Favaro's work is better understood when we learn that he spent forty-four years in his study of the life and works of Galileo.

The "History of Anatomical Injections" in the seventh chapter, by J. H. Cole, should be of profound interest to every student of medicine. The eighth chapter is written by F. S. Marvin on "Science and the Unity of Mankind" and is a masterly production. F. S. Conybeare appears in the succeeding chapter with an article entitled "Four Armenian Tracts on the Structure of the Human Body," which is of considerable historic value. The eleventh chapter is written by F. C. Schiller on "Hypothesis." J. M. Jenkinson has written about "Science and Metaphysics," while the thirteenth chapter contains a "Sketch of the History of Paleobotany," by E. A. Newell Arber.

J. M. Child has given a delightful criticism of "Archimedes's Principle of the Balance." Arthur Platt contributes the last and fifteenth chapter, with the title, "Aristotle on the Heart." There is in addition an appendix and index covering twenty-six pages.

The book is excellently written, is clear in style and illustrated generously with plates and figures, which are unsurpassed. It is only necessary for one to read the entire list of contributions in order to obtain an idea of the scope of the work. One readily realizes after reading this book what a debt medicine owes to the ancient Greeks and the prominent scientific men through the Middle Ages, for the great contributions which they have made and which are used today as the foundations for a great many of our classifications, ideas and methods in scientific work. It seems that the Greeks were prone to the same errors as modern writers, in that they gave results of experimental work without instructing the reader as to the means by which they came to their conclusions.

Nothing but praise can be given in the way of criticism on this book, and every medical man will find in it facts concerning the origin and development of scientific principles, gathered together in one volume, which it would take him a great amount of time to find or read were he to search for the same independently. P.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND

ROGER S. MORRIS, M.D.,

FREDERICK FORCHHEIMER PROFESSOR OF MEDICINE IN THE UNIVERSITY OF CINCINNATI, CINCINNATI, OHIO,

AND

THOMAS ORDWAY, M.D.,

DEAN OF UNION UNIVERSITY (MEDICAL DEPARTMENT), ALBANY, N. Y.

Bismuth in the Treatment of Syphilis. — CLEMENT SIMON and J. BRALEZ (*Bull. méd.*, 1922, **36,** 523) review the recent literature regarding the treatment of experimental and human syphilis with various salts of bismuth, the most important of which is sodium and potassium tartro-bismuthate. The first Congress of Dermatology and Syphilis, which just took place at Paris, devoted a whole session to reports of investigations with these drugs. The authors report their own experience in the treatment of 113 cases of syphilis with the insoluble bismuth salts. They employed four different preparations of sodium and potassium tartro-bismuthate. The route of the administration was intramuscular, the drug being given in oily suspension. The dosage was 20 cg., each injection being given twice a week, a course of treatment consisting of from 6 to 12 injections. The authors find that the reactions from the use of this drug are in general those described by previous investigators. The most important reaction is stomatitis, which occurred in about 12 per cent of all cases treated. In a somewhat higher proportion of cases, however, there appears also a bluish line on the borders of the teeth and large bluish spots on the internal surface of the cheeks, this pigmentation being similar to that observed in chronic lead poisoning. In practically all instances the stomatitis was mild and cleared up promptly on the cessation of bismuth treatment. An additional 12 per cent of patients developed reactions of other types during the course of treatment, these reactions being for the most part cramps, malaise, nausea, headache, and a single reaction simulating nitritoid crisis after arsphenamine. In general, reactions of all types

were mild and did not interfere to any great extent with the treatment. So far as the therapeutic results are concerned, treponemes disappeared within two to fourteen days from chancres and from the mucous lesions of secondary syphilis. Chancres were healed in the average of fourteen days after a total of 4 injections, whereas the lesions of secondary syphilis healed in an average of twenty-two days after 6 injections. A number of cases of latent Wassermann positive syphilis were treated, but the authors conclude that too little time has elapsed to permit any evaluation of the serologic results. Their impression is that bismuth acts less rapidly than arsphenamine on the Wassermann reaction. They treated 3 cases of cerebro-syphilis and 7 of tabes dorsalis. In several of these there was notable improvement in clinical symptoms, but no change occurred in the cerebrospinal fluid findings. They conclude that the salts of bismuth may prove to be of great value in the treatment of syphilis, particularly in those cases, unfortunately too common, which are intolerant of arsphenamine and mercury.

Absorption of Digitalis in Man.—CARY EGGLESTON and JOHN WYCKOFF (*Arch. Int. Med.*, 1922, **30,** 133) report upon the rate of absorption of especially purified tincture of digitalis and of various official tinctures of the same drug. With the exception of certain details, the results agree with previous work of Eggleston and others upon the therapeutic dosage of digitalis in proportion to body weight. The conclusions are not in accord with a report of Wedd who found that: "No constant relation between the amount of digitalis that could be given and the age or body weight of the patient or the condition of the myocardium could be discovered." Eggleston and Wyckoff used in most of their work a chloroform soluble extract of digitalis in alcohol, which they call a "purified tincture." With this preparation the greatest total range of variation in effective dosage was between 23 per cent below and 21 per cent above the average dosage. In this respect the purified tincture was more uniform than "official" tinctures. The absorption of the purified tincture was two to three times as rapid as that of galenic tinctures. It was found that tincture of digitalis shows definite evidences of action on the heart in from two to four hours after oral administration to man. Evidence is offered to show that digitalis causes nausea or vomiting in man by reflexes arising in the heart as a result of the intoxication. The authors advocate doses of digitalis more conservative than those formerly suggested. It is now believed that 0.1 cat unit of the drug per pound of body weight of the patient represents fairly well the average full therapeutic dose.

Diastolic Activity of the Heart.—SIEWERT, A. K. (*Ztschr. f. d. Ges. Exp. Med.* 1922, **28,** Hefte 5 und 6) divides diastole into two distinct parts and produces experimental evidence to show that there is an active phase of diastole late in the long period of the heart's cycle. Observations were made upon the interventricular pressure throughout systole and diastole by exposing an animal's heart and inserting a recording manometer directly into the ventricle. It was found that under ordinary conditions there is comparatively little negative pressure within the ventricle, whereas this negativity may be increased by 200 or more per cent by cardiac stimulation, for example, by injecting

strophanthin into the pericardium. Siewert considers that the relative activity of diastole at any particular moment can be measured by the degree of negative pressure that obtains within the ventricle. The point at which the greatest negativity begins he calls D, and electrocardiographic studies have shown that D corresponds to the beginning of auricular systole. He, therefore, concludes that the heart participates actively in its own filling during a short phase at the end of ventricular diastole. Such a theory of cardiac mechanism may have considerable bearing upon the mode of production of presystolic gallop rhythm and presystolic murmurs.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY AND ASSOCIATE IN SURGERY IN THE UNIVERSITY OF PENNSYLVANIA; SURGEON TO THE PHILADELPHIA GENERAL AND NORTHEASTERN HOSPITALS AND ASSISTANT SURGEON TO THE UNIVERSITY HOSPITAL.

Epithelioma of the Genitourinary Organs.—Broders (*Ann. Surg.* 1922, **75,** 574) says that epithelioma of the genitourinary organs occurred more often in females than in males; the proportion was about three to one. Approximately 12 per cent of the author's series had a family history of malignancy. The average duration of the lesion in all of the patients was 1.35 years. Over 90 per cent of the patients were operated upon. Twenty-three per cent of all the patients are alive with good results while 70.5 per cent obtained poor results, living for an average of 1.34 years. Ten per cent of patients with large cervical lesions obtained good results, while 33 per cent of those with medium-sized lesions had good results. One hundred per cent of patients with small lesions obtained good results. In all, 20 per cent or one in five obtained good results, with cervical lesions. Patients with lesions of labia show relatively the same percentages. Forty-eight per cent or nearly one-half of the patients with lesions of the bladder obtained good results, while 41 per cent of patients with lesions of the penis obtained good results.

Hernia of the Bladder.—Baker (*Ann. Surg.*, 1922, **75,** 615) says that the majority of bladder hernias are in fact false hernias as they either have no peritoneal sac at all or the bladder is found alongside the hernial sac instead of within the sac. According, therefore, to the manner in which the peritoneum is involved in these bladder hernias the classification is given as extraperitoneal, paraperitoneal and intraperitoneal (or true bladder hernia). The possibility of bladder involvement should always be suspected and due caution observed in all large inguinal hernias, more especially those of advanced life and in those manifesting prostatic hypertrophy or other signs of crippled bladder

were mild and did not interfere to any great extent with the treatment. So far as the therapeutic results are concerned, lesions disappeared within two to fourteen days from chancres and from the mucous lesions of secondary syphilis. Chancres were healed in an average of fourteen days after a total of 6 injections, whereas the lesions of secondary syphilis healed in an average of twenty-two days after 6 injections. A number of cases of latent Wassermann positive syphilis were treated, but the authors conclude that no little time has elapsed to permit any evaluation of the serologic results. Their impression is that bismuth acts less rapidly than neoarsphenamine on the Wassermann reaction. They treated 3 cases of cerebro-syphilis and 7 of optico-luesis. In several of these there was notable improvement in clinical symptoms, but no change occurred in the cerebrospinal fluid findings. They conclude that the salts of bismuth may prove to be of great value in the treatment of syphilis, particularly in those cases, unfortunately too common, which are intolerant of neoarsphenamine and mercury.

Absorption of Digitalis in Man.—Olney Eggleston and Wyckoff (*Arch. Int. Med.*, 1922, 30, 133) report upon the rate of absorption of especially purified mixture of digitalis and of various official mixtures of the same drug. With the exception of certain details, the results agree with previous work of Eggleston and others upon the therapeutic dosage of digitalis in proportion to body weight. The conclusions are not in accord with a report of Weed who found that "No constant relation between the amount of digitalis that could be given and the age or body weight of the patient or the condition of the myocardium could be discovered." Eggleston and Wyckoff used in most of their work a chocoform soluble extract of digitalis to which they call a "purified mixture." With this preparation the greatest total range of variation in effective dosage was between 2 per cent below and 2 per cent above the average dosage. In this respect the purified mixture was more uniform than "official" mixtures. The absorption of the purified mixture was two to three times as rapid as that of galenic mixtures. It was found that mixtures of digitalis show definite evidences of action on the heart within two to four hours after oral administration to man. Evidence is offered to show that digitalis causes nausea or vomiting in man by reflex action from the heart as a result of the intoxication. The authors advocate doses of digitalis more conservative than those formerly suggested. It is believed that 11 cat units of the drug per pound of body weight of the patient represents fairly well the average full therapeutic dose.

Diastolic Activity of the Heart.—Stewart, H. K. (*Johns Hopkins Hosp. Bull.*, 1922, 33, 1) reports a study of diastolic changes in different parts and produces experimental evidence to show that there is an active phase of diastole and in the dog period of the heart cycle. Observations were made upon the interventricular pressure throughout the cycle and diastole by exposing an animal's heart and inserting a recording manometer directly into the ventricle. It was found that under ordinary conditions there is comparatively little negative pressure within the ventricle, whereas this negativity may be increased by 200 or more per cent by cardiac stimulation, for example, by injection

[illegible] auricular systole. He, therefore, considers that the heart participates actively in its own filling during a short phase at the end of ventricular diastole. Such a theory of cardiac mechanism may have considerable bearing upon the mode of production of presystolic pulsation and presystolic murmurs.

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[illegible] BY [illegible]

E. H. BENER THOMAS, M.D.

[illegible] SURGEON TO THE [illegible] AND ASSISTANT SURGEON TO THE [illegible]

Epithelioma of the Genitourinary Organs.—Shennan (Ann. Surg., 1922, lxxv, 571) says that epithelioma of the genitourinary organs occurred more often in females than in males, the proportion was about three to one. Approximately 2 per cent of the author's cases had a family history of malignancy. The average duration of the lesion in all of the patients was 1.23 years. Over 90 per cent of the patients were operated upon. Twenty-three per cent of all the patients are alive with good results while 70.6 per cent obtained poor results, living on an average of 1.24 years. Ten per cent of patients with large cervical lesions obtained good results, while 33 per cent of those with medium-sized lesions had good results. One hundred per cent of patients with small lesions obtained [illegible] per cent of those in five obtained good [illegible] Patients with lesions of labia show [illegible] Ninety-eight per cent of patients [illegible] of the bladder obtained good results, [illegible] lesions of the penis obtained good [illegible]

[illegible] Surg., 1922, lxxvi, 655) says that [illegible] not take [illegible] the other [illegible] is found alongside the [illegible] Therefore, to the [illegible] bladder hernia, the [illegible] and [illegible] of bladder diverticula [illegible] observed in all large [illegible] advanced life and in those [illegible] cases of crippled bladder

function; in all direct inguinal hernias regardless of size or age; in all operations for recurrence of hernia, for recurrences are notoriously of the direct type and adhesions about the neck of the sac from the former operation result in a possible pull on and displacement of the bladder. In all hernias presenting an undue amount of fatty tissue closely associated with the sac, at or near the fovea inguinalis medialis, the possibility of injury to the bladder is increased and this danger signal should never go unheeded.

The Cause of Death in High Intestinal Obstruction.—Ellis (*Ann. Surg.*, 1922, **75**, 429) says that in cases of high obstruction a poison can be isolated by precipitation with alcohol, extraction with boiling water and reprecipitation with the aid of magnesium sulphate. It is not possible to obtain such a poison with this method from the intestinal content of a normal dog prepared immediately after removal. A poison which, when judged by the means at the author's disposal, is identical, can be obtained from conditions other than actual obstruction, such as the intravenous injection of the obstruction toxin into normal animals, the removal of the adrenals, portal obstruction and in experimental acute non-bacterial peritonitis. This poison is undoubtedly elaborated in the cells of the greater part of the mucosa of the small intestine but chiefly in those of the duodenum. It is manifestly excreted partly into the lumen of the intestine, but the larger part passes into the lymph stream. The clinical similarities between acute pancreatitis and high obstruction are due either to a close relationship between the toxins involved or possibly to the fact that acute pancreatitis actually produces conditions in the intestinal mucosa favorable to the production of the same toxin as is found in cases of high obstruction. Since erepsin fails to exert any action upon the toxin and since the toxin shows no lymphagogic action whatever, it seems necessary to conclude that the toxin is neither a proteose nor a heteroproteose. The finding of the toxin in the intestinal content after the removal of the adrenals suggests that clinically adrenalin should be added to the saline infusion.

Non-tuberculous Kidney Infections.—Sullivan (*Ann. Surg.*, 1922, **75**, 473) says that the kidney is the eliminating organ for circulating bacteria and in the course of this elimination may itself be damaged in a variety of ways. Hematogenous infection may be restricted not only to a single kidney but even to a circumscribed portion of the organ. The source of the infection may not only be a general disease but a distant and apparently insignificant focus may be responsible. Metastatic hematogenous infection of the kidney, perinephritic or paranephritic abscess, is not always easily recognized and may be confused with intraabdominal infections. A sudden attack of pain in the kidney region associated with fever in a patient known to have a suppurative process elsewhere in the body should excite suspicion of metastatic kidney infection. Cystoscopy and pyelography are valuable aids, especially when urinary changes are incomplete or the symptoms are referred to the healthy side. The treatment of perinephritic or paranephritic abscess is early drainage. When the suppuration involves the kidney parenchyma or where the process is an acute fulminating one, nephrectomy is indicated.

Tuberculous Empyema.—HEDBLOM (*Surg., Gynec. and Obst.*, 1922, **34**, 445) says that primary or idiopathic pleurisy with effusion in a large proportion of cases is probably tuberculous in nature. A past history of pleurisy with effusion is common in cases of tuberculous empyema. In many cases the effusion is serous at the onset. Tuberculous pleurisy may be primary or it may be secondary to a pulmonary, peritoneal or other tuberculous lesion. The onset of a tuberculous effusion may be insidious or it may be sudden and associated with an acute and severe constitutional reaction. A mixed pleural infection due to the perforation of a tuberculous cavitation often runs an acute and rapidly fatal course. Diagnosis of tuberculous empyema is made by demonstration of the bacilli in the exudate, by animal inoculation or by examination of the sectioned pleura. A sterile effusion is probably tuberculous. An infected effusion may be tuberculous. Empyema following primary idiopathic pleurisy with effusion or empyema of insidious onset, especially in the presence of a pulmonary or other tuberculous condition, is probably tuberculous. Empyema may be tuberculous in spite of persistently negative findings over a long period of time. In a closed pleural cavity a sterile effusion, whether serous or purulent, should not be treated by open drainage except in the presence of an impending perforation of the chest wall. Repeated aspiration of only part of the fluid present is indicated in cases of serous effusion, producing definite dyspnea on exertion or symptoms of circulatory embarrassment. The replacing of aspirated fluid by nitrogen or filtered air may be indicated in cases in which there are symptoms of active phthisis referable to the same side as the effusion. A sterile purulent effusion should be treated as though it were serous if the lung expands when fluid is withdrawn. If the lung is fixed in a collapsed condition or if the effusion persistently recurrs an extrapleural plastic operation is indicated. Effusion in a closed cavity showing a mixed infection should be treated by the closed method with antiseptic solution irrigation or by open drainage; the open drainage is indicated especially in cases of severe infection associated with extensive pulmonary tuberculosis, making irrigation hazardous. Tuberculous empyema with a large bronchial fistula should be drained by the open method. A plastic operation involving closure of a bronchus offers the only prospect of a cure in case of an associated large bronchial fistula. An extrapleural rib resection is indicated for the collapse of closed sterile cavities. Cases of long standing associated with greatly thickened pleura require an extensive resection of the entire chest wall after the method of Schede.

Human Actinomycosis.—MATTSON (*Surg., Gynec. and Obst.*, 1922, **34**, 482) says that there is but one true species of microörganism capable of producing actinomycosis in man and lower animals, and this is the one indicated by Wolff and Isreal and later more fully described by Wright. There is no convincing clinical and biological evidence that this microorganism has its source outside of the human body; as a saprophyte in old sod soil from which it gains access to grains and grasses and through this medium or intermediary host, so to speak, it becomes capable of infecting man and lower animals. In order for infection to take place two things are necessary: first, an abrasion of the tissues; second, the

fungus must in some way be brought directly in contact with this abrasion. Human actinomycosis is not a rare disease but a disease which is often overlooked or incorrectly diagnosed. Every inflammatory swelling of chronic or subacute nature with persistent and recurring sinus formation should be carefully investigated for this disease. The disease should always be kept in mind in every case of a typical pulmonary tuberculosis and should be looked for in cases suffering with chronic purulent bronchitis. Early treatment of superficial lesions are highly successful. Internal infections are extremely fatal and hopeless.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,
OF PHILADELPHIA.

The Relation of Nutrition and Tooth Development and Tooth Preservation.—McCollum, Simonds, Kinney and Grieves (*Bull. Johns Hopkins Hosp.*, 1922, **33**, 202) studied this problem in rats. They found that the internal structure of the skeleton of the rat could be changed at will by varying the ration which the animals received. Bone is an extremely labile tissue and is readily influenced by nutritional environment. Some of the faulty diets which were studied produced rickets often of an exaggerated type, while others caused osteoporosis. Still others resulted in the development of the peculiar lesion which has been called osteosclerosis. A study of the effect of these diets on the skeleton would indicate that the growth of the skeleton was dependent on at least three substances: (1) an organic substance present in certain fats, which is not identical with the antixerophthalmic fat-soluble A; (2) calcium; (3) phosphorus. If the organic factor is low in, or missing from, a diet, the structure of the osseous tissue is dependent on the ratio between the other ions in the circulating blood. If calcium is present in amounts equal to or exceeding those which would be optimal for growth and function, if all other factors are satisfactory but the phosphorus ion is low, rickets is produced. The same disease results when the converse relation exists between the two ions. In other words, diets which contain optimal or excessive amounts of calcium but are low in phosphorus and the organic element produce rickets. This is also produced from diets low in calcium and the organic element although phosphorus is present in satisfactory amounts. Diets which are satisfactory except that they are deficient in the organic substance result in osteoporotic but perfectly calcified bone. Diets which have a comparative deficiency in calcium but are very high in phosphorus and in the organic substance produce the so-called osteosclerotic bone, with large numbers of small trabeculæ which are imperfectly formed. Diets deficient in calcium alone produce a pseudorachitic condition with overproduction of osteoid.

Thymus Apoplexy.—Wahl and Walthall (*Am. Jour. Dis. Child.*, 1922, **24**, 27) report 2 cases which they classify as examples of this rather unusual manifestation of hemorrhagic disease of the newborn. The 2 cases were similar in many respects. Symptoms of meningeal irritation, lateral nystagmus, and generalized icterus were present in both babies. Labor was not normal, but was not unduly difficult or prolonged in either case. In both cases there was a marked increase in the coagulation time of the blood. In each case the necropsy showed a cerebral hemorrhage, inflammatory changes in the lungs suggestive of syphilis, and a diffuse hemorrhagic infiltration of the thymus in which the extravasation of the blood was both intralobular and interlobular, and was associated with suppuration necrosis and marked proliferation of the reticular epithelial cells. The cases differ in that the second case was much older than the first. The hemorrhages were more generalized in Case 1, and labor was more difficult. The immediate cause of death of this case was cerebral hemorrhage, while in the other bronchopneumonia was probably the more immediate factor causing death. There was a considerable organization of the hemorrhage in Case 2, indicating an older process than in Case 1 in which no new capillaries or fibroblasts were found. In both cases the Hassall's corpuscles were numerous, but in Case 1 they were dilated, and often contained a purulent exudate, forming early DuBois abscesses. On the other hand Case 2 showed a striking perivascular inflammatory reaction with swelling of the vascular endothelium, and also marked thrombophlebitis of the smaller veins. In Case 1 one of the large veins was partly occluded by a thrombus. The relation of these cases to syphilis is exceedingly interesting. Case 1 presented no positive clinical findings. The Wassermann tests on the bloods of both the father and the infant were negative. No examination of the mother's blood could be made. Several members of the family showed constitutional weakness and syphilis could not be excluded even with negative blood findings. The clinical findings in Case 2 were more suggestive of syphilis. The Wassermann test of the blood of the mother was strongly positive but in the case of the child was negative. There was no opportunity to repeat this test and a single negative test is not conclusive. The anatomic changes in both cases, while not pathognomonic, afford strong presumptive evidence of syphilis. The interstitial inflammatory changes in both lungs suggest syphilis. The lobules of the thymus that are not disintegrated by hemorrhage show changes in both cases that are regarded as characteristic of congenital syphilis. In both cases there was marked reticular epithelial cell proliferation, associated with more or less atrophy of the thymic lymphocytes, which has been noted by a number of authors as a characteristic change in the thymus of congenital syphilis. The etiology of thymus apoplexy is obscure. So few cases have been reported that final judgment cannot be made. It is probable that one or more of four factors play a part in each case. Circulatory stasis especially in the thymus in which marked hyperplasia exists may be a cause. When this is the main factor the hemorrhage is diffused throughout the gland giving the appearance of a hemorrhagic infarct. A second factor is trauma. A third factor is the presence of hemorrhagic disease of the newborn, that is, a defect in the coagulation mechanism of the blood. This hemorrhagic tendency

is frequently associated with, if not due to, some underlying infectious process analogous to hemorrhages in the medulla of the suprarenal so commonly found in the newborn. The fourth and probably the most important factor is the role played by infectious diseases, especially syphilis. It is common to find small petechial hemorrhages in the thymus in pneumonia in infants. Undoubtedly the hyperemia associated with an infection predisposes to hemorrhage. The fact that necrosis and suppuration preceded the hemorrhage in both of the cases reported, makes the presence of an infection, probably syphilis, most likely.

Food Requirements in Newborn Infants.—FABER (*Am. Jour. Dis. Child.*, 1922, **24**, 56) thinks that appetite provides a fairly accurate index of the needs of the newborn infant. In his series of 85 cases and with the formulas he used it appeared also to be a safe guide in so far as the avoidance of dangers to the digestion is concerned. The demands of the infants for food exceeded the basal requirements on the second day, equaled the average total requirements of Benedict and Talbot on the third day. On the fifth day they rose to the Heubner optimum of 100 calories, and thereafter rose slowly to about 115 calories near the end of the second week. That these demands are not excessive is indicated by the weight curve which, avoiding a greater initial loss than can be accounted for by mechanical factors, showed the same rate of gain as was previously established for healthy infants in the same community. The author sounds a warning that the method he describes, adopted for a special purpose, is not advocated for general use with breast-fed infants. It may be well that for the conservation and increase of mammary secretion a period of partial starvation during the first weeks is useful or even necessary.

The Food Requirements of Children: Carbohydrate.—HOLT and FALES (*Am. Jour. Dis. Child.*, 1922, **24**, 44,) continue the investigations of the food requirements of the young in a study of the carbohydrate requirement. They found that carbohydrate is a desirable and probably an essential component of food for children, although it does not have any specific function in nutrition. It forms the largest part of the diet of all periods of life. Nursing infants take on an average of about 12 gm. carbohydrate per kilogram of body weight daily. Artificially fed infants usually receive somewhat more than this. The carbohydrate in the diet of an infant is almost entirely sugar, that of the nursing infant entirely lactose and that of the artificially fed infant usually a mixture of lactose with saccharose or maltose and dextrin. The carbohydrate intake of more than one hundred healthy children from one to eighteen years of age, studied by the authors, averaged 10 gm. per kilogram. Of this, 51 per cent was sugar, including lactose, saccharose and fructose, and 49 per cent was starch. Carbohydrate is more economical than fat or protein, both commercially and physiologically. Because of the first-named advantage, there is a growing tendency to increase the proportion of the carbohydrate in the diet beyond the amount which is desirable. When a very large proportion of the food is in the form of carbohydrate, the intake of fat and protein or both is likely to be less than the normal nutritive need of the body. A diet excessive in carbohydrate leads to an abnormal deposition of fat

and without a corresponding increase in muscular development. Children taking such a diet have a feeble resistance to infection. There is no evidence that a relationship exists between the high proportion of the carbohydrate in the modern diet and the prevalence of dental caries. Definite digestive disturbances, chiefly intestinal, may be produced when the carbohydrate in the diet is excessive. There may result increased fermentation with loose acid stools or constipation with flatulence and abdominal distention. When long continued these disturbances are very difficult to control. Carbohydrate furnishes the calories needed in the diet which are not supplied by the requisite amounts of fat and protein. It seems rational to allow in the diet of the child of average activity about 12 gm. of carbohydrate per kilogram of body weight at one year, decreasing this amount to about 10 gm. per kilogram at six years and maintaining it at this value throughout the remainder of the growth period. An increase in the total caloric need may be supplied by the carbohydrate alone.

Gastric Findings in Children with Anorexia.—Sauer, Minsk and Alexander (*Jour. Am. Med. Assn.*, 1922, **79**, 184) observed that the average emptying time of the stomach for twelve children with good appetite was four and a half hours. In twenty-one children with poor appetite the emptying time was six and one-tenth hours. The stomachs of the twelve children first mentioned were empty in five hours while in the other group sixteen still had retention at the end of five hours. All but one of the twenty-one children with poor appetite had an original emptying time longer than that found to be the average for the children with good appetites. The average total hydrochloric acid for the twelve children with good appetite was 61.2, the free acid was 26.3. For eighteen with poor appetite the total acid was 49.4, and the free acid 14.9. In two children of the group with poor appetite, free acid was absent on examination and upon reëxamination months later, while their emptying times were not especially long. Eleven of the twelve children of the first group were of the sthenic habitus. Sixteen of the twenty-one children of the other group were of the hyposthenic or asthenic habitus. In a number of asthenic children, the emptying time of the stomach and the amount of the acid were influenced beneficially by proper measures and this was reflected by an increase of appetite and weight.

The Difficulties and Practicability of Infant Feeding in a Country Practice.—Simpson (*Penna. Med. Jour.*, 1922, **25**, 782) sums up the difficulties as superstition, ignorance, the fancied self-sufficiency of mothers of large families and the absence of ice and clean milk. It will be remarked that many of these difficulties are not limited to the country practice. He points out that there is one definite superstition, which is found chiefly among the Pennsylvania Dutch, and which is applied to malnutrition, rickets, or any chronic disease characterized by loss of weight or failure to gain weight. Such conditions are all spoken of as the "take off," and often long before a physician is consulted such a case is "powwowed" or measured with a tape by some member of the laity, who is supposed to be able to cure this condition, which is looked upon as a mysterious disease that no method of feeding or medical treatment can cure.

OBSTETRICS

UNDER THE CHARGE OF

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Concealed Hemorrhage Complicating Pregnancy.—WILLSON (*Surg., Gynec. and Obst.*, 1922, **34**, 57) describes a case of albuminuria and edema in a pregnant hospital patient, from whom a clear history could not be obtained. After a gestation period of about seven months, there was a shoulder presentation and heart sounds could be made out on the right side of the abdomen, comparatively low. On estimating the size of the mother, it was found that the pelvis was a little under the average. The patient was admitted to the hospital for the treatment of toxemia and grew considerably better. When labor came on, uterine contractions were vigorous, and after several hours of labor there was vaginal hemorrhage with vomiting, nausea and epigastric pain. This became very severe, with tenderness on palpation, and shock and hemorrhage, which steadily increased, and there was pronounced pain on palpating the abdomen, and when the uterus was palpated it did not relax but seemed to be in tonic contraction. The size and location of the child could not be made out but a presenting part seemed to be at the brim of the pelvis. It was impossible to hear the heart sounds. There was no evidence of labor, no dilation of the cervix, and on introducing the finger a placenta could not be felt. It seemed evident that the placenta was more or less loosened. Section was undertaken as soon as possible, and on opening the abdomen a serous, bloody fluid was found in abundant quantity. The appearance of the uterus was unusual, as it was dark bluish-black in color, with areas of different appearance; this abnormality being most pronounced at the left upper portion. On examining the uterus more carefully both anterior and posterior walls presented this unusual condition. Extending in a longitudinal direction there were depressions in the uterus where the muscular tissue had separated without involving the peritoneum. There seemed to be no abnormality in the ovaries and tubes. When the uterus was incised on the left side, the afterbirth was found in front and loosened from its attachment, so that but two-thirds of the placenta was still attached. There were several pints of fluid blood in the uterine cavity and a considerable quantity of clot. It was possible to extract through the abdominal wound the entire fetal mass without rupturing the membranes. The operator did not perform a hysterectomy, and as the patient showed some shock, salt solution was given hypodermically. Unfortunately abortion was unsuccessful and had been undertaken too late, the patient surviving but a few hours. A postmortem examination revealed considerable change in the substance of the liver,

which was less firm and lighter in color than the average. The gall-bladder, bowels and stomach seemed normal, but there was some softening in the spleen. The kidneys resembled the liver in the lighter color and softer consistency. The tubes and ovaries were normal, but over the surface of the utervs, under the peritoneal covering, blood had extravasated and a similar condition was present in the left broad ligament. On sectioning the uterus, its muscle was found entirely lacking in tone and firmness, and there were degenerated areas between the individual muscle fibers. On microscopic examination of the liver lobules, necrosis had advanced to a considerable degree in the center of each lobule. This was shown by the staining and by beginning fatty degeneration. A similar process had involved the kidneys and also the uterine muscle. In the latter, blood had been exuded in considerable quantity amid the muscle fibers. On gross examination there was nothing abnormal in the placenta. In the villi hyaline degeneration was present in no very marked degree. In addition to and including his own, the author reports 69 cases. The theory that concealed hemorrhage and separation of the placenta arise from mechanical violence to the uterus, he discards, nor does he accept uterine distention or hyperemia of the wall of the uterus as a sufficient cause for separation of the placenta. The theory that failure of the uterus to permit escape of blood causes placental separation is not adequate. For some time there has been developing a tendency on the part of obstetricians to consider the toxemia of pregnancy as the essential element in producing the condition under discussion. If we are to rely upon the teaching of pathology, there is a remarkable likeness between the condition of the tissues in these cases and that seen in the bodies of animals dying from the bites of serpents. It has long been known that in many patients eclampsia has preceded accidental hemorrhage. Hence, it is at once suggested that an important factor is common to both and that high blood-pressure may be a common cause. So far as the recovery of the patient is concerned, there must always be a considerable mortality and morbidity. The writer gives a death-rate of 38 per cent in 50 patients under observation, in whom he made a diagnosis before operation of the condition. A complication so grave must greatly increase the chance of fetal death, and in 67 cases under the observation of the writer the mortality was 92.5 per cent. It must not be concluded that death inevitably follows the accidental separation of the placenta in all cases, nor that all patients who have this complication require abdominal section. Where, however, there is evidence of considerable disturbance in the patient's pulse, temperature and respiration, operation should be done as soon as possible. The majority of observers agree that Cæsarean section is the preferable operation. Hysterectomy should never be done unless the conditions present imperatively demand it and the preservation of the uterus would increase the risk to the mother's life. Many of these cases show a tendency to continue to bleed after the uterus has been emptied. In many others there must be a supposition that infection

is present. Under these circumstances the operation known as the Porro hysterectomy is safest. The writer's study of the subject has led him to believe that what he terms apoplexy of the uterine and placental tissues results from the abundant discharge over the endometrium and in the substance of the uterus of a toxic material which forms during hemorrhage. This substance seems to be produced by the placenta and hence the tissues at the site of the placenta are most often attacked. That variety of bleeding which sometimes occurs, and in which it may be impossible positively to demonstrate the cause of the complication, is considered by the writer to be a part of the same process. In many cases so badly weakened is the wall of the uterus by these toxins that bleeding occurs into the abdominal cavity, and also from the uterus after it has been emptied. In those cases where the complication develops rapidly without dilatation of the cervix or labor, and where evidently the bleeding is severe, there is no choice of method but Cæsarean section, with total extirpation of the uterus or hysterectomy, as indicated.

The Condition of the Membranes and Especially the Epithelia of the Amnion in Cases of Premature Rupture of the Membranes.—HEINLEIN (*Monatsschr. f. Geburtsh.*, 1922, **56**, 237) alludes to an account, already published, giving the examination of the membranes in cases of premature rupture where it seemed evident that a violent inflammation of the amnion and chorion, causing necrobiosis, was possibly the cause of the premature rupture. Cervical endometritis was evidently the cause of the inflammation preceding the rupture of the membranes. The writer has studied 27 cases of premature rupture of membranes, and 12 cases of membranes ruptured at the usual time, to observe the microscopic condition in both: His investigations came practically to the same conclusion as those already quoted. In the 27 cases there was an active inflammation of the membranes with destruction of cells in 5 cases. The process was less active and severe in 9, but feebly developed in 4; while there was considerable hemorrhage in the deeper layers of the membranes, with or without inflammation, in 7 cases. In 2 cases no pathological condition could be found, although there was a considerable deposit of cellular material, which made it hard to find the site of the rupture. It is important to find the point of rupture, because the pathological process is most active at that point. As one proceeds further away from the point of rupture in the membranes the pathological process becomes more or less indistinct. This seemed to disappear in the vicinity of the placenta where the membranes join the afterbirth. Only in those cases where the primary rupture of the membranes occurred near the border of the placenta did the characteristic pathological changes appear, and occasionally this inflammatory process attacked a small portion of the placenta. A genuine inflammation of the placenta with small cell infiltration, in or between the villi, was not observed. The writer recognized the amnion and the layer of cells beneath the chorion, which often contains degenerate villi and other remains of the decidua. Where inflammation was most pro-

nounced the structure of the membranes could not be made out, and the tissues normally present were replaced by small homogeneous masses without nuclei. At other portions necrosis was evidently present with round-cell infiltration and leukocytes and the epithelium of the amnion had practically disappeared. The degree of necrosis depended upon the violence of the inflammation. Where the inflammation was but slight its site was in the tissues between the amnion and chorion. Bleeding was present in a few cases only, and in some where hemorrhage was most copious there was no evidence of inflammation. The site of bleeding was usually the decidua. Near the tissue the bloodvessels were dilated and increased, and the walls of the vessels were so thinned that in some places they could not be recognized. The blood made its way between the layers of the membranes. In some cases blood pigment was present, but this is sometimes seen in normal cases. In some cases of inflammation of the chorion and amnion, these were attacked before the epithelium of the amnion was inflamed. In other cases masses of granular material were found above the epithelium of the amnion; the cells were not only greatly altered but in some places had disappeared with the development of cylindrical epithelium in masses with wide spaces between. Where necrosis occurred the nuclei had disappeared and the form of the epithelial cells could not be made out. In 25 of the 27 cases in which the membranes had ruptured prematurely there was a very essential change in the membranes. This change was an inflammation (recent or of some duration) with a necrotic process often accompanied by hemorrhage, hemorrhage being sometimes present without inflammation. This process was usually seen in the layers underneath the chorion, while hemorrhage usually occurred in the decidua. In all cases the epithelium of the amnion was affected. It seems evident that these changes in the membranes have something to do with premature rupture and that the integrity of the amnion depends upon the condition of its epithelium. The epithelial cells are usually firm and resisting and influence the formation of the fibers of the amnion. It will be remembered that the amnion has no bloodvessels and that it is nourished from the deeper tissues beneath. If a pathological process attacks these deeper tissues the epithelium of the amnion will immediately suffer, the fibers of the amnion are not properly formed and the membranes will rupture without especial violence. One can readily appreciate that, if the membranes rupture sometimes before delivery, bacteria may make their way into the uterus and set up an inflammation of the membranes; but in some cases the time between the rupture of the membranes and delivery is too short for these changes to occur. The changes in the membranes must have taken place by some previous process. In a case of abortion at four months the embryo was removed with unruptured membranes from the uterus. Microscopic examination of the membranes showed a severe inflammation throughout the entire membranes with extensive necrosis. As to the existence of a previous endometritis the writer is unable to make a positive statement. As slight inflammation of the decidua is often found in membranes otherwise normal, what the element is which

extends this inflammation to the layer between the chorion and amnion is not clear. An inflammation of the placental substance itself with small-cell infiltration and infiltration between the villi of the chorion could not be clearly demonstrated in any case.

GYNECOLOGY

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Action of Salicylates on the Uterus.—Many text-books of pharmacology mention that abortion sometimes occurs during the treatment of acute rheumatism with salicylates, but that it is uncertain which of these factors is the cause. Therefore in order to determine more definitely the relationship existing between the drug, the disease and abortion, GUNN and GOLDBERG (*Jour. Pharmacol. and Exper. Therap.*, 1922, **19,** 207) performed experiments which showed that salicylate of soda has a definite stimulating action on the uterus, but that this action is not powerful; for instance, on the isolated uterus it is only half as strong as sodium carbonate and possibly less than one-fortieth as strong as quinine hydrochloride. It was noticed that when large doses were gradually introduced into the blood, as occurs when salicylates are given therapeutically by mouth, the stimulation of the uterus was much less marked. The stimulation did not appear to these investigators to be so pronounced as to suggest that it is likely to be of any great importance in the production of abortion, however, when salicylates are administered clinically very wide variations are found in the amounts given before toxic symptoms appear, and it is not impossible that there may also be considerable differences in the amounts necessary to influence the uterus. Acute rheumatism is practically universally treated with salicylates and these investigators conclude that if salicylates had a greater abortifacient action than their experiments show, the incidence of abortion in rheumatic fever would be greater than it is. In fact since the effect of salicylates is so apparent on rheumatic fever and so slight on the uterus, it is possible that the reason why fewer miscarriages are seen in rheumatic fever than in the other acute fevers is because of the rapid control of the former by sodium salicylate.

Effect of Radiation on the Blood.—The results of the analysis of the experiments performed by LEVIN (*Am. Jour. Roentgenol.*, 1922, **9,** 112) to determine the action of radium and roentgen rays on the blood and

the blood-forming organs tends to confirm the prevailing opinion that the lymphocyte is the most radio-sensitive cell in the animal organism. The change in the numerical relationship of the two types of white cells was not accompanied by a noticeable change in the total leukocyte count. Apparently the mechanism of the action of the rays on the leukocytes of the blood consists in the destruction of the lymphocytes, which is then followed by the release of the polymorphonuclear leukocyte from the bone marrow or by an overproduction of this type of cell by the blood-forming organs. Certain investigators maintain that the polymorphonuclear leukocytes are the type of the blood cells most readily destroyed by the rays. However, the analysis of their results shows that the destruction of the polymorphonuclear leukocytes only takes place as the final result of the action of a lethal dose of the rays which produces ultimately a severe general leukopenia. In the present investigation however, only such amounts of radium and roentgen-ray were given that the animals could completely recover after the lapse of a certain time and the blood picture again become normal. The most important phenomenon observed in the course of this study is the difference with which the two species of animals, the frog and the rabbit, react to the action of radium and the roentgen-ray. In the frog the same general effect was obtained on the blood by the amount of roentgen raying employed in this investigation, as well as by the insertion of a glass capillary containing 1.0 to 9.6 millicuries of radium emanation. The blood of the rabbits reacted to the roentgen-rays in a manner identical with that of the frog. On the other hand, an insertion into the spleen or the bone marrow of a rabbit of 2 or 4 capillaries, that is, 2 or or 4 times the amount of radium emanation inserted into the frog, produced no change in the blood of the rabbit, though it produced marked local effect on the spleen and bone marrow. These comparative findings in the two species of animals and the two types of radiation are of considerable importance to the subject of radiotherapy from the two following standpoints: The subjects of the relative therapeutic efficiency of radium and roentgen-rays of the higher or lower voltage of the electric current producing the roentgen-rays, of the correct methods of physical measurements of the rays, whether photographic or ionization methods, for instance, and the correct amounts to be used, are in the order of the day. However, these subjects are treated chiefly from the standpoint of physics rather than from that of biology. There cannot be any doubt that measured by photography and ionization methods or generally considered from its physical aspect one roentgen-ray application as employed in the present investigation and one capillary tube containing 1.0 (or less) millicuries of radium emanation inserted into the frog and left there to decay represent two qualitatively and quantitively different entities. Nevertheless they must be considered quite analogous biologically, since they produce the identical effect on the blood of the frog. This indicated clearly that for biology and medicine a biological standard of measurement would be of far greater value than the physical methods. It may be added that the action of the rays on normal blood and lymphoid tissue is of greater importance than their action on the skin, the more so that the radium and roentgen-ray burns are most probably due to the change in the lymphoid tissue of the walls of the bloodvessels. The second phenomenon observed in

this investigation further illustrates the importance of the biological differences for the ultimate result of the action of the rays. The roentgen-rays produce a change in the blood picture of the rabbit because the square surface of its body is greater than that of the frog, and consequently the former receives a greater amount of radiation, though all the other conditions of the roentgen-ray apparatus were the same as those used in the frog. The radium emanation tubes produced no change in the blood of the rabbit, though the amount was more than sufficient to produce a change in the blood of the frog. The reason for it lies in the fact that the effect is distributed in the larger quantity of the blood of the rabbit and becomes so small as not to be perceptible. At the same time the local effect of the radium emanation is very marked. Two conclusions may thus be drawn from the analysis of the experiments. First, that radium, as compared with roentgen-rays will produce the same and even a more marked local effect with far less general disturbance of the blood. Second, that the larger the square surface of the entry of the roentgen-rays into the organism the more severe is the general effect on the blood.

Trichomonas Vaginalis Vaginitis.—The presenting symptom of trichomonas vaginalis vaginitis, according to the experience of HARTWELL (*Colorado Med.*, 1922, **19**, 86), is a vaginal discharge which is so irritating as to be "scalding" to the skin with which it comes in contact and so profuse as to necessitate the wearing of a napkin; it is so perversely persistent as to fail to respond to ordinary measures. The scalding of the skin is often so severe that the patient is handicapped in the performance of her duties by day and the associated pruritus is so intense that her night's sleep is disturbed. During the menstrual period however, the irritation and itching usually subside. In addition to this the discharge is frequently so malodorous that it interferes with the patient's social activities. When a patient presenting these symptoms is examined it is often noted that the skin on the inner aspect of the thighs and over the perineum is reddened, if not eroded, by the irritating vaginal discharge. On spreading the labia the vestibule is usually bathed with a thin white secretion and the mucous surfaces of the labia minora and the carunculæ myrtiformes may present minute bright red macules, while occasionally small condylomata stud the labia. When the speculum is introduced, there is seen in the vault a quantity of puriform secretion notably full of bubbles, and this secretion may be superlatively malodorous. On removing it, the vaginal mucosa presents the beefy red appearance of any vaginitis if the process be acute, or is quite normal in color if the process is chronic. In either case however, the characteristic raised papules, irregularly scattered over the mucosa are in evidence. They may be solitary or aggregated in small groups and not infrequently the apices of the papules are eroded, presenting superficial ulcers of small size which may bleed. The appearance presented by the vaginal mucosa is strongly suggestive of a dermatitis produced by a chemical irritant such as iodine, or the early lesions of a herpes zoster. The reaction of the vagina is very strongly acid. Such appearances are almost pathognomonic of a trichomonas vaginalis vaginitis, but the diagnosis is confirmed by the microscopic examination of a small bit of the bubbly secretion when large numbers

of motile flagellated trichomonades are easily recognized. In treating this condition, HARTWELL has obtained the most satisfactory results by placing soda bicarbonate powder in the vaginal vault. The following morning the patient takes a douche of plain water. In the afternoon the treatment is repeated. Daily treatments are required for about two weeks and every second day for another four weeks before the vagina is free from trichomonades. The principle of the treatment is to maintain the reaction of the vagina strongly alkaline, which alkalinity seems to be inimical to the life and growth of the trichomonas vaginalis.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Complement-fixation Tests in the Diagnosis of Tuberculous Infections.—The results obtained by various investigators, employing the complement-fixation test in tuberculous infections have not been concordant and observers have differed from each other in the percentage of positive findings in cases of definite tuberculosis, as well as in their views concerning the diagnostic and prognostic value of the test. Realizing that such divergencies can be attributed in part to differences in the technic used, SELLERS and RAMSBOTTOM (*Jour. Path. and Bacteriol.*, 1922, **25**, 247) conducted numerous complement-fixation tests on the blood and spinal fluid of adults and the blood of children with and without clinical evidence of tuberculosis, and obtained results which agreed, on the whole, with those of other observers. Seven different strains of tubercle bacilli were used for preparing five antigens found useful by other workers. Accordingly, 3 of these antigens were employed in comparative tests on 40 adult cases of pulmonary tuberculosis which yielded from 75 to 90 per cent positive according to the antigen, 40 cases of bone tuberculosis, where 50 to 55 per cent were positive and 15 cases of non-syphilitic spinal fluids in which the positives varied from 6 to 33 per cent. Varying percentages of negatives were encountered in undoubted cases of tuberculosis and a few non-tuberculous sera gave positive reactions. Moreover, nearly one-half the cases of syphilis in children in which there was no clinical evidence of tuberculosis gave a positive tuberculosis test. In 13 cases of non-tuberculous spinal fluid, 4 were positive and 9 negative; in 12 cases of meningitis in which there was a suspicion of a tuberculous origin, 6 were positive and 6 negative and in 11 cases of tuberculous meningitis, all were positive. As a result of their investigations, the authors "are not satisfied that

complement-fixation tests afford a reliable means of clinical diagnosis in tuberculosis cases." They believe that "too little attention has been paid to the so-called non-specific reactions." They think, however, that possibly complement-fixation tests may thrown some light on the pathology of tuberculosis.

The Fat of Adipose Tissue in Malignant Disease.—Following the observations of Duncan that a decided difference existed in human fat before and after puberty, the low percentage of 4.47 of non-saturated fatty acids between nine and eleven years of age being replaced by the higher one of 60.88 from sixteen to nineteen years, and that a similar increase takes place in the fat of cancer patients (the percentage rising from 61.1 in health to 72.62 in that disease), CURRIE (*Jour. Path. and Bacteriol.*, 1922, **25**, 213) investigated the condition of the fatty tissues in cancerous patients and the presence, or otherwise, of any pigments or special pigment in it and cancerous tissue. Iodine values were determined in 33 specimens of fat, of which 8 were from sarcomata, 21 from carcinomata and 2 were from chronic inflammatory lesions and 2 from normal cases. Although Duncan found that the adipose tissue fat in cancer, no matter in what part of the body it was stored, exhibited a constancy in iodine value, the present work indicates that unsaturation finds its highest expression in fats adjacent to carcinomata with sarcomata coming next, whereas there is a constancy in iodine value of *normal* adipose tissue fat from any part of the body. It was found "that the hydrogenation of fat varies inversely with the degree of pigmentation, the pigment probably acting as a catalytic inhibitant, so that if the fat is highly pigmented and also highly unsaturated it exhibits a greater slowness in adjusting itself to corresponding body conditions than if the degree of pigmentation were lower. Adipose tissue is at any moment in delicate equipoise, two opposed and balancing reactions (saturation and unsaturation) proceeding simultaneously, the net result being dependent on the concentration of the respective enzymes."

Further Investigations of Disturbances of Blood-sugar Equilibrium in their Relation to Neoplasia.—Working with rats, ROHDENBURG, KREHBIEL and BERNHARD, (*Jour. Cancer Research*, 1921, **6**, 223) by ablating the various endocrine organs as kidney, thyroid, thymus, spleen, adrenals, pancreas, testes or ovaries either singly or in all two gland combinations and determining the blood-sugar values after injection of a 1 per cent heterologous protein (beef peptone) in doses of 0.5 cc or by previously inoculating extracts of liver, pituitary, pancreas, adrenal and thyroid in another group, found that the disturbance of blood sugar equilibrium which follows the injection of a protein varied in intensity and type; that the removal of certain of the endocrines influenced both the intensity and type of the reaction and that neither the intensity nor the type of the reaction had any relation to the strength of the antibody development after the injection of the selected protein. With the idea of clinical application, a large series of human beings, suffering from various diseases, were injected with homologous proteins (blood serum or ascitic fluid) and the sugar content of the blood was ascertained. It was learned that in diseases involving the gastro-

intestinal tract, duodenal ulcer excepted, and in diseases involving the gall-bladder and liver 88 per cent of all cases of neoplasia showed a reaction of less than 12 mgm. The authors indicate that, if the endocrine relationship which they outlined in the first part of their investigations be accepted, such a lessened reaction would suggest, either spleen, adrenal or gonad insufficiency, or thyroid, adrenal or pancreas overactivity. They believe that the observation concerning the blood-sugar equilibrium in gastro-intestinal neoplasia is possibly of value as a diagnostic procedure.

The Supposed Importance of Vitamins in Promoting Bacterial Growth.—McLeod and Wyon (*Jour. Path. and Bacteriol.*, 1921, **24**, 205) investigated the relations, if any, which existed between vitamins and bacterial growth with a view to use the bacterial growth as an index of the presence of vitamins in research upon the latter. The effect of materials containing "water soluble B" upon *S. aureus* and *B. dysenteriæ* (Shiga) was determined by the use of a simple phosphate-agar medium to which the various extracts and chemical substances had been added. Many of the results were compatible with the vitamin hypothesis. There was a large discrepancy between the two guinea-pig kidney extracts, seemingly due to an unknown inhibitory substance in one of them. The figures for bran and milk were very low. The same of milk was of the "separator" type and possibly inhibitory substances were present. Comparison of amino-acid content with potency negatived the idea that the results were entirely due to amino-acids and the suggestion that nucleic acid or its congeners were responsible for the results was not substantiated by experiment. A comparison of the chemical and physical properties of the staphylococcus stimulant of yeast with those of "water soluble B" revealed serious discrepancies. An attempt was made, also, to determine the nature of the property of fresh blood or serum by virtue of which it promoted the growth of delicate bacteria, such as pneumococcus and meningococcus, by inoculating a series of tubes of bouillon to which additions of blood, serum and other substances had been made from dilute emulsions of the bacteria. It was learned that the growth promoting power did not bear any definite ratio to the known vitamin contents and that this growth promoting power for pneumococci was to some extent destroyed by heating serum, etc., whereas that for meningococci was altered but little or enhanced. It was also found that the growth promoting quality of 1 per cent peptone agar plus serum was very little enhanced by the addition of tryptic digests where pneumococcus, meningococcus and hemolytic streptococcus were concerned and that high concentrations of amino-acid readily inhibit the growth of these organisms. On the other hand, tryptic digests favored the growth of the bacteria of the bowel. No satisfactory evidence that the growth promoting factor for bacteria can be extracted by alcohol could be obtained, the power of promoting growth inherent in the serum being, apparently, a phenomenon of the colloid state.

The Diurnal Variation in the Sizes of Red Blood Cells.—Price-Jones (*Jour. Path. and Bacteriol.*, Cambridge, 1920, **23**, 371) found that there was a gradual increase in the diameter of red cells during the day

and a diminution during the night; that violent exercise increased these changes, whereas gentle exercise had no apparent influence; that rest in bed did not abolish the diurnal variations and that after forced breathing the diameters of the red cells were diminished. The method of examination consisted in making films from blood obtained by pricking the finger or ear, drying in the air without heat, fixing and staining in Jenner stain for two minutes and afterward for two minutes in a weak aqueous solution of eosin. Some convenient form of projection apparatus was then arranged to project the image of the microscopic field on to a sheet of paper lying on the table and adjusted for a magnification of 1000 diameters. The red cells were outlined in pencil, two diameters (maximum and minimum) were measured to 0.5 mm. and the mean of these measurements was accepted as the diameter of the cells. The cells were classed into groups, progressing by 0.25 μ, and the mean diameter of 500 cells was taken to represent the mean diameter of the red cells for any specimen of blood. The author states that his observations "suggest that the variations in size of the red cells are due to differences in the reaction of the blood, but whether the diminished alkalinity and increased diameters which prevail during the active part of the day are due to accumulation of CO_2 or lactic acid, or to some other source of altered reaction, we have at present no means of judging."

The Carbohydrate Metabolism of Surviving Mouse Tissues and Tumors. — RUSSELL (*Brit. Jour. Exper. Path.*, 1922, **3**, 51) reports a continuation of his previous work with Woglom, (*Ibid.*, 1920, **1**, 244) having to do with the gaseous exchange of surviving tissues of the mouse and particularly the determination of the ratio of carbonic acid output to oxygen intake, that is, the respiratory quotient. By measuring the changes in volume observed in an air space containing a known quantity of finely divided tissue or tumor, it was found that significant differences occurred in normal kidney, liver, breast, submaxillary gland and embryo and still greater differences were encountered in six strains of transplanted tumors, the respiratory quotient of the more rapidly growing tumors being higher than that of the more slowly growing ones. By adding small amounts of different sugars to the tissue emulsion before placing it in the respirometer bulb, it was ascertained that "the low respiratory quotient observed with slowly growing transplanted tumors was not attributable to their incapacity of burning glucose; that mouse tumors and tissue appeared capable of dealing with the common sugars in a very similar manner, provided the sugars were supplied directly and that differences in the quantity of sugar within the cells was a probable explanation of the variations in the carbohydrate metabolism of tumors growing at different rates."

The Histology of Destructive Changes in Icteric Livers.—In a histological study of the livers from 7 human cases of grave mechanical jaundice, which furnished convincing illustrations of destructive changes caused by the retention of bile, SCHWARZ (*Jour. Path. and Bacteriol.*, 1922, **25**, 207) found that the stasis produced a dilatation of the biliary capillaries with tearing in the inter- and intracellular endings of the fine biliary vessels. The liver cells showed only slight degenerative metamorphoses as long as the thrombi formed only casts within the capil-

laries. After these latter burst, the thrombi became coiled up and part of the bile diffused into the surrounding tissue. It was thought improbable that these distorted thrombi fused into the large golden yellow lumps of bile found next to the trabeculæ but that they probably were formed within the trabeculæ when the latter were rapidly destroyed by polycholia combined with obliteration of biliary ducts. The portions destroyed by the larger clumps of bile with subsequent imbibition of the tissue usually exhibited remnants of pigment in the detritus cavities. There was hardly any leukocytic infiltration nor many marked extravasation for blood because of the rather slow destruction which seemed to permit of extensive regeneration. As soon as a few cells were destroyed they were replaced by new ones. The production of connective tissue between the acini was apparently initiated by fibroblasts, although it was not clear that a regular granulation tissue was a forerunner of the connective tissue strands. No actual enclosure of biliary thrombi in phagocytic cells could be observed.

The Production of Coliform Infection in the Urinary Tract of Rabbits.—In order to produce lesions in the kidney by intravenous injection of coliform organisms, so as to examine the inflammatory changes produced soon after infection so that the path of the bacilli through the kidney might be studied, LEPPER (*Jour. Path and Bacteriol.*, 1921, **24**, 192) performed a series of experiments upon rabbits by injecting various strains of *B. coli communis*, *B. coli communior* and *B. acidi lactici* into the ear vein in different dosages with and without complete obstruction to the urinary flow by ureteral ligation over varying lengths of time. When the coliform bacilli appeared in the urine after intravenous injection, there was, with one exception, evidence of concomitant kidney changes as shown by the presence of albumin, or pus, epithelium and bacilli in the urine. The sequence of events following intravenous injections, so far as they could be traced in microscopical sections, was first, a bacillary embolus of capillary vessels, generally those of the papilla, followed by a round cell infiltration in the connective tissue surrounding the affected vessels. If the infection was severe, the inflammation extended to the tubules and in some cases necrosis of the tip of the papilla occurred. The complete obstruction of the urinary flow from a kidney for so short a period as fifteen minutes was adequate to make it vulnerable to coliform organisms circulating in the blood. The mode of production of these lesions was probably hemorrhage into the kidney from dilated veins caused by pressure of the distended pelvis on the renal vessels. There was some evidence that the type of inflammation resulting from blood infection combined with obstruction to the urinary flow was more severe than that produced by blood infection alone. Severe infections of the connective tissue in the vicinity of the kidney did not spread very rapidly to that organ, but if a blood infection resulted from the septic focus a renal lesion sometimes followed.

Experiences with the Schick Test and Active Immunization Against Diphtheria.—COPEMAN, O'BRIEN, EAGLETON and GLENNY (*Brit. Jour. Exper. Path.*, 1922, **3**, 42) continued investigations into the value of the Schick test and active immunization against diphtheria upon the personnel of an institution where the population was a very stable one.

Of 329 children between the ages of three and sixteen years, among whom a recent epidemic of diphtheria had occurred, 18 (6 per cent) carried morphological B. diphtheriæ in throat or nose. At the end of the epidemic 5 per cent carriers were found which decreased to 2 per cent, two months later. Twelve cultures of the 18 children were isolated, 5 of which were virulent. The authors believe that the avirulent carrier is of no epidemiological importance and that the danger of a carrier of virulent bacilli is proportionate to the number of virulent organisms present in throat and nose, and therefore, to the ease with which the virulent bacilli can be isolated. Of the 329 children, 102 (31 per cent) gave a positive Schick reaction. Ninety-five per cent of the readings made on the first day were accurate. Of 203 children who were retested two months later, 201 gave the same reaction. Ninety-eight per cent of 102 Schick-positive children who received toxin and antitoxin mixture, gave negative or negative and pseudo reactions eleven weeks later.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Investigations on the Control of Hookworm Disease. I. General Introduction.—W. W. Cort (*Am. Jour. Hyg.*, 1921, **1**, 557) in this paper gives an analysis of some of the factors involved in hookworm control and points out some of the unsolved problems in connection with the life of the hookworm in the soil. He emphasizes the following conceptions: (1) That the object of hookworm campaigns is rather to reduce the number of worms in a population than to cure individuals completely, (2) that the factors involved in the spread of hookworm disease in different situations are so complex and differ so in different localities that each control project must be considered as an independent problem, and (3) that an adequate study of the sources of human infestation in an area will aid greatly in the development of control measures. The author further points out that little is really known of the life of the hookworm outside the body in its natural environment on account of the difficulty of studying the larvæ in the soil. The development of an apparatus by Baermann which makes it possible to isolate hookworm larvæ from the soil makes it possible to attack effectively a number of problems on this stage. An outline is given which suggests a number of lines along which investigations need to be directed in the study of the life of the hookworm outside the body.

II. The Description of an Apparatus for Isolating Infective Hookworm Larvæ from Soil.—W. W. CORT, J. E. ACKERT, D. L. AUGUSTINE and FLORENCE K. PAYNE in this paper (*Am. Jour. Hyg.*, 1922, **2**, 1–16) make their first report of investigations carried on in Trinidad, British West Indies, on hookworm disease under the joint auspices of the Department of Medical Zoölogy of the School of Hygiene and Public Health of Johns Hopkins University and the International Health Board of the Rockefeller Foundation. It gives a description of Baermann's apparatus as used in the work of this expedition, an account of the results obtained in isolating hookworm larvæ from the soil with this apparatus under a variety of conditions, and some suggestions as to how it can be utilized in hookworm investigations and control work. By the use of the apparatus as described in this paper it was possible to isolate nematodes from considerable quantities of soil. It was found to be possible to distinguish mature hookworm larvæ both sheathed and unsheathed from other nematodes found in the soil, by their characteristic structure and movement. Experiments to standardize the apparatus showed: (1) That to isolate a satisfactory percentage of the larvæ the water must be warmer than the soil, (2) that a slightly higher percentage of the larvæ present can be isolated from moist than saturated soil, (3) that a larger percentage of the larvæ can be isolated from coarse soil than from that with finely divided particles, and (4) that while most of the larvæ escape from the soil in the first six hours an appreciable percentage come out after this time.

III. A Discussion of the Finding of Unsheathed Hookworm Larvæ in the Soil.—W. W. CORT, D. L. AUGUSTINE, J. E. ACKERT, FLORENCE K. PAYNE and G. C. PAYNE (*Am. Jour. Hyg.*, 1922, **2**, 17) report the finding that a large proportion of the mature hookworm larvæ isolated from soil samples brought in from infected spots in the field and from experiments in soil had lost their protective sheaths. The conclusion is reached that it is a common thing for mature hookworm larvæ to lose their sheaths and to continue to live in the soil. This finding will probably make it necessary to revise many of our conceptions in regard to the life of the infective hookworm larvæ in the soil since it was thought always to live enclosed in a sheath.

IV. The Relation of the Domestic Chicken to the Spread of Hookworm Disease.—On account of the extent to which the domestic chicken ingests human feces, especially under tropical conditions, its relation to the spread of hookworm infestation is a matter of considerable importance. J. E. ACKERT (*Am. Jour. Hyg.*, 1912, **2**, 26) studied this problem experimentally and found (1) that eggs of the human hookworm can remain viable while passing through the alimentary canal of chickens and can later hatch and develop in chicken feces. It was found, however, that the great majority of hookworm eggs ingested by chickens fail to produce infective larvæ. Spots of soil infestation could be established around drinking fountains by chickens which had been fed hookworm eggs day after day. Newly hatched hookworm larvæ passed through the digestive tract of the chickens alive, but infective larvæ which were fed the chickens were not found

in the feces. The author concludes that a comparison of the reduction in infective hookworm larvæ after ingestion by fowls with the danger of the establishment of infective spots by them, convinces him that chickens are more beneficial than harmful in the control of hookworm disease in Trinidad.

V. The Domestic Pig and Hookworm Dissemination.—J. E. ACKERT and FLORENCE K. PAYNE (*Am. Jour. Hyg.*, 1922, **2**, 39) conclude from a series of experiments that a high percentage of the eggs of human hookworm swallowed by domestic pigs are able to produce infective larvæ, and that the free-range pig is an important factor in the dissemination of human hookworm eggs. A preliminary description is given of Necator suillus n. sp., which was found to be common in the domestic pigs of Trinidad, B. W. I.

VI. A Study of the Effect of Hookworm Control Measures on Soil Pollution and Infestation in a Sugar Estate.—W. W. CORT and G. C. PAYNE (*Am. Jour. Hyg.*, 1922, **2**, 107) in this paper make an intensive epidemiologic study of an area in a sugar estate in Trinidad, British West Indies, to determine the exact sources of human infestation and to learn the effect on soil pollution and soil infestation of the control campaign. Of the 142 East Indians and negroes living in barracks on this area 117, were found by fecal examination to be infected with hookworms. Control measures were instituted as in the International Health Board campaigns in the West Indies including educational measures, the building of latrines and a series of three treatments. Before the introduction of the control work soil pollution was wide spread and very gross, being especially concentrated at certain easily accessible places near the edge of a cane field near the barracks where the people lived. Examinations for infective hookworm larvæ of soil samples taken from this area showed very heavy soil infestation at the places of soil pollution in the cane field, but very little pollution near the barracks or in the yards. It was found that hard packed clay-loam soil when without vegetation was not favorable for the development of hookworm larvæ. The localized character of the soil infestation, especially in the cane field, showed that there was but little active migration of the infective hookworm larvæ from their places of development, although the examinations from the drains showed that they were carried a considerable distance by water. The study of the habits of the people of this area, in relation to the distribution of soil infestation, suggested that most of their infestation must have come from the habit, which so many of them had, of visiting certain places in the cane field for the purpose of defecation. Surveys in the cane field showed a great reduction of soil pollution after the building of an adequate number of latrines and the carrying on of an educational campaign. After the reduction of soil pollution in the strip along the edge of the cane field and the treatment of the people of the area, series of samples taken at intervals showed a rapid dying out of infective hookworm larvæ from this area, so that in about six weeks soil infestation was practically eliminated.

VII. An Epidemiologic Study of Hookworm Disease in a Cacao Estate.—W. W. Cort and G. C. Payne (*Am. Jour. Hyg.*, 1922, **2**, 149) find that people living in three unselected houses on a cacao estate in Trinidad, British West Indies showed a heavy infestation with hookworms. Soil pollution in this area was almost entirely restricted to definite spots—"natural latrines"—in the cacao grove near the barracks studied. The examination of soil samples for infective hookworm larvæ showed very little soil infestation anywhere in the area, except at the "natural latrines" in the cacao, and the conclusion can be drawn that almost all the human infestation must have come from the visits to the pollution spots in the cacao. Examinations of the soil of the intensely polluted spots in the cacao, six weeks after three routine treatments had been given to the people, showed a very marked reduction of soil infestation, indicating that in this situation the life of the infective hookworm larvæ is short.

VIII. Experiments on the Migration of Hookworm Larvæ in Soils.—D. L. Augustine (*Am. Jour. Hyg.*, 1922, **2**, 162) shows in a series of experiments in which mature hookworm larvæ were studied in the soil, that they did not migrate actively in periods varying from fifteen hours to forty-two days. It was shown, however, that hookworm larvæ may be carried out from centers of soil infestation by surface water, and that they can establish themselves in the new locations when the water recedes. Soil scraped from the shoes of men who had passed through places of intense soil infestation was found to contain numbers of infective hookworm larvæ, suggesting another method of distribution. The conclusion is drawn that soil infestation is much more limited to the places of soil pollution than was generally supposed.

IX. On the Position of the Infective Hookworm Larvæ in the Soil.—D. L. Augustine (*Am. Jour. Hyg.*, 1922, **2**, 172) found that infective hookworm larvæ under optimum conditions of moisture and temperature remain on or very near the surface of the soil. They creep up pieces of wood, decaying vegetation, and other objects, only as far as the film of moisture extends; but are not found in drops of water on the leaves of green plants. At centers of soil infestation in the field where the surface is covered with leaves or twigs, the larvæ are found on the leaves or twigs when they are moist, but as the vegetation dries the larvæ retreat to the soil below.

X. Experiments on the Length of Life Life of Infective Hookworm Larvæ in Soils.—D. L. Augustine (*Am. Jour. Hyg.*, 1922, **2**, 177) reports a series of laboratory experiments on the length of life of mature hookworm larvæ in soils of various types (clay-loam and sand), which showed a great reduction in numbers of larvæ occurring within two or three weeks, a fairly constant small percentage of the larvæ remaining alive up to seven weeks and a complete dying out after that time. The loss of the sheath in the soil was not found to shorten the life of the mature larvæ under favorable conditions. Unsheathed larvæ were able to penetrate the skin of an experimental rat. The conclusion was drawn that environmental conditions such as tropical temperatures, which tend to increase the activity of the mature hook-

worm larvæ, will shorten their lives by the more rapid using up of the stored food material. It is evident from the experiments recorded in this paper and from the studies in the field recorded above that under tropical conditions, at least, the length of life of the mature hookworm larvæ in the soil is much less than was previously supposed.

XI. Vertical Migration of Infective Hookworm Larvæ in the Soil. (Preliminary Report).—Florence K. Payne (*Am. Jour. Hyg.*, 1922, **2**, 254) found that in clay-loam soil in which the distribution of moisture was uniform, buried hookworm larvæ did not migrate upward more than two inches. In saturated soil on which water was standing there was a high death rate of larvæ and little migration. In experiments with clay-loam soil in which the conditions of rising ground water were stimulated, there was a considerable migration of buried larvæ, 74.4 per cent of those recovered having migrated three inches or more, 15.4 per cent more than five inches and a few more than seven and a half inches. A distinct reduction in the stored food granules of the intestinal wall was noted in larvæ after vertical migrations of only an inch or two and almost a complete loss of these granules came about in those which had migrated five or six inches. This loss of stored granules in larvæ which had migrated different distances is clearly shown in a series of eleven photomicrographs. This series is very suggestive since it shows how quickly intense activity will reduce the food reserve in infective hookworm larvæ.

The Prevention of Tuberculosis. Theory and Possibilities.—Lewis (*Am. Rev. Tuberc.*, 1922, **6**, 229) states that it would seem evident that tuberculosis, whether bovine or human in type, is alike gained for the most part during early childhood; that either type may be activated and reactivated by all forms of pathogenic microörganisms; and that the balance or resistance of the infected individual is measured by the defects of the individual in their relation to air and food metabolism. Such factors have ever been submerged in the various theories of attack on prevention. Prevention has been accomplished by prevention of the activation of the tubercle bacillus by uncontaminated water and protection against filth-borne diseases like hookworm infection. The subjection of recurring cyclic frequencies of respiratory diseases, notably through the streptococcus, alike the activator and complicator of those specific diseases as well as tuberculosis, and the correction of anatomical defects of human beings are further essential factors. As evidenced by epidemiology and vital statistics, the path of the many into the one and the one into the many of Aristotle takes direct cognizance not of the tubercle bacillus only as the path, but rather as one of the many in the direct prevention of tuberculosis.

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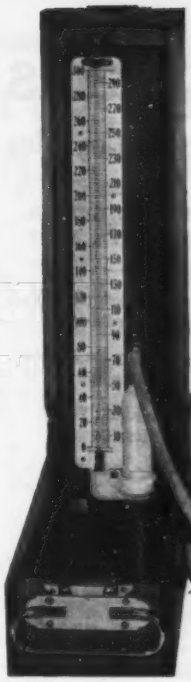

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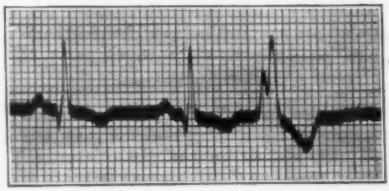

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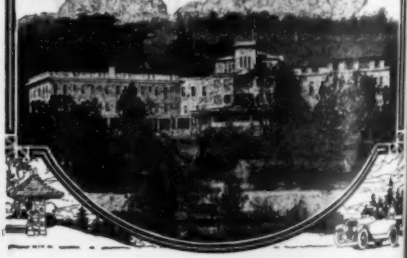

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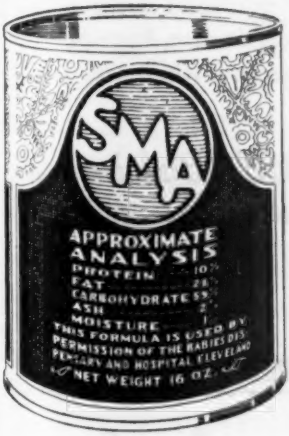

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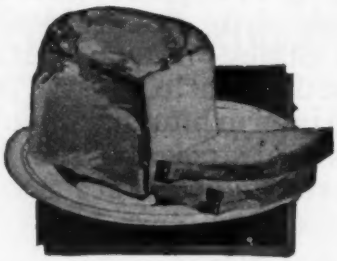

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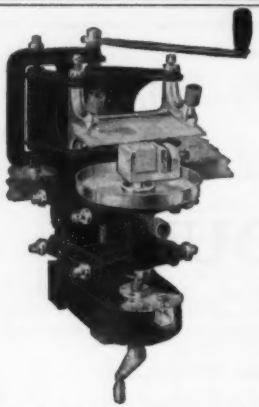

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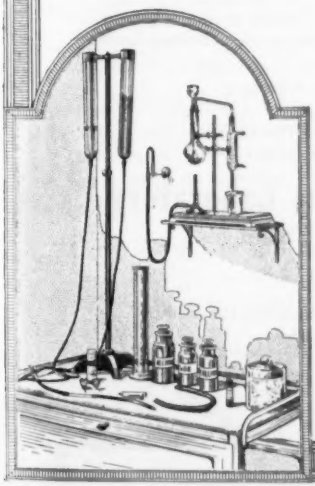

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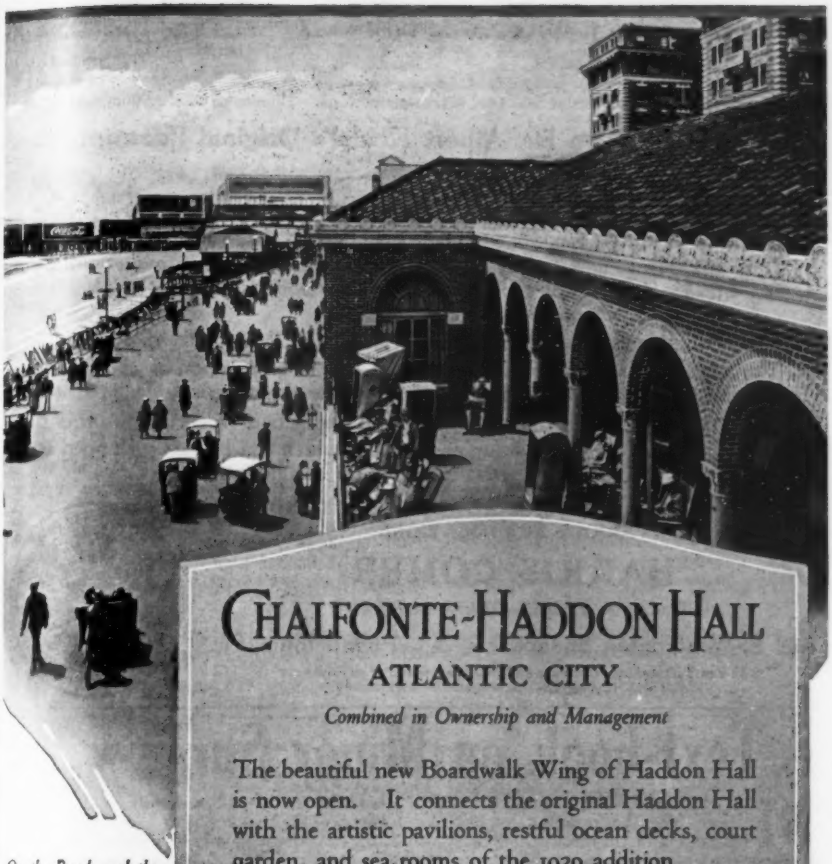

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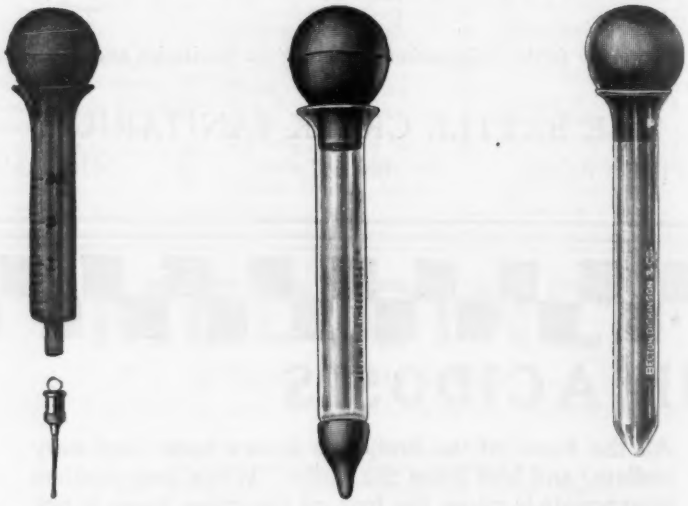

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THE COLONIAL, MOUNT CLEMENS, MICHIGAN
(MOUNT CLEMENS SANITARIUM COMPANY)

Specific Antigens Prepared From Standardized Cultures of Known Origin

FOR THE PHYSICIAN WHO DEMANDS
ACCURATE, SCIENTIFIC THERAPY

AT YOUR DRUGGISTS

or from

Chemists Supply Company
61-63 East Lake Street, Chicago, Ill.

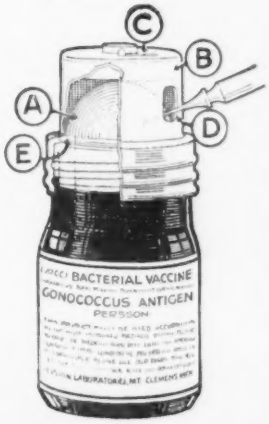
C. F. Knight Drug Company
Century Building, St. Louis, Mo.

F. G. Roddy, 202 Proctor Building, Troy, N. Y.

Leopoldo Venegas, San Juan, Porto Rico

GENERAL DISTRIBUTORS

A–Hollow rubber stopper.
B–Aseptic pad. C–Stop for outer cap.
D–Opening for insertion of needle.
E–Flange of rubber stopper hermetically sealing bottle.



The Management of an Infant's Diet

Malnutrition, Marasmus or Atrophy

Mellin's Food
4 level tablespoonfuls
Skimmed Milk
8 fluidounces . .
Water
8 fluidounces . .

Analysis:

Fat . . .	.49
Protein . . .	2.28
Carbohydrates . .	6.59
Salts . . .	.58
Water . . .	90.06
	100.00

The principal carbohydrate in Mellin's Food is maltose, which seems to be particularly well adapted in the feeding of poorly nourished infants. Marked benefit may be expected by beginning with the above formula and gradually increasing the Mellin's Food until a gain in weight is observed. Relatively large amounts of Mellin's Food may be given, as maltose is immediately available nutrition. The limit of assimilation for maltose is much higher than other sugars, and the reason for increasing this energy-giving carbohydrate is the minimum amount of fat in the diet made necessary from the well-known inability of marasmic infants to digest enough fat to satisfy their nutritive needs.

Mellin's Food Company, Boston, Mass.

The Premier Digitalis

Digifoline, "Ciba"

The Digitalis which gives you results when others fail

According to actual experiences of physicians DIGIFOLINE, "CIBA" *will stand this test*

Physiologically Standardized

Tablets and Liquid
For Internal Use

TRADE C B A MARK REGISTERED

Ampules
For Subcutaneous and Intravenous Use

Ciba Company
INCORPORATED
CEDAR AND WASHINGTON STS. NEW YORK CITY